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5d. PROJECT NUMBER

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14. ABSTRACT
This research program develops block copolymer thin films as model systems for understanding protein activity in the immobilized state and as effective technologies to achieve optimal protein activity on surfaces.

15. SUBJECT TERMS
polymer surface, protein

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a. REPORT	b. ABSTRACT	c. THIS PAGE			Xiaoyang Zhu
UU	UU	UU	UU		19b. TELEPHONE NUMBER 212-851-7768

Report Title

Final report: Controlling Protein Conformation and Activities on Block-Copolymer Nanopatterns

ABSTRACT

This research program develops block copolymer thin films as model systems for understanding protein activity in the immobilized state and as effective technologies to achieve optimal protein activity on surfaces.

Enter List of papers submitted or published that acknowledge ARO support from the start of the project to the date of this printing. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

Received		Paper
04/08/2012	1.00	Lei Shen, X.-Y. Zhu. Evidence of a Mobile Precursor State in Nonspecific Protein Adsorption, Langmuir, (05 2011): 0. doi: 10.1021/la200602v
04/08/2012	2.00	Lei Shen, Athena Guo, Xiaoyang Zhu. Tween surfactants: Adsorption, self-organization, and protein resistance, Surface Science, (03 2011): 0. doi: 10.1016/j.susc.2010.12.005
09/11/2012	6.00	Lei Shen, Xiaoyang Zhu, Adam Garland. Mobile precursor mediated protein adsorption on solid surfaces, Progress in Surface Science, (01 2012): 1. doi: 10.1016/j.progsurf.2012.02.001
09/11/2012	7.00	Lei Shen, Adam Garland, Yini Wang, Zicheng Li, Christopher W. Bielawski, Athena Guo, X.-Y. Zhu. Two Dimensional Nanoarrays of Individual Protein Molecules, Small, (07 2012): 0. doi: 10.1002/smll.201200673
09/11/2012	8.00	Lei Shen, Takuji Adachi, David Vanden Bout, X.-Y. Zhu. A Mobile Precursor Determines Amyloid-? Peptide Fibril Formation at Interfaces, Journal of the American Chemical Society, (08 2012): 0. doi: 10.1021/ja305398f
TOTAL:	**5**	

Number of Papers published in peer-reviewed journals:

(b) Papers published in non-peer-reviewed journals (N/A for none)

Received		Paper
TOTAL:		

Number of Papers published in non peer-reviewed journals:

(c) Presentations

A mobile precursor determines amyloid-? peptide fibril formation at the liquid-solid interface, ACS National Meeting, September 2012.

Number of Presentations: 1.00

Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received Paper

TOTAL:

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received Paper

TOTAL:

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts):

(d) Manuscripts

Received		Paper
04/08/2012	3.00	Lei Shen, Takuji Adachi, David Vanden Bout, X.-Y. Zhu. A mobile precursor determines amyloid-? peptide fibril formation at the liquid-solid interface, Nature Chemistry (01 2012)
04/08/2012	4.00	Lei Shen,, Adam Garland,, Yini Wang,, Zicheng Li,, Christopher W. Bielawski, , Athena Guo, X.-Y. Zhu. Two Dimensional Nanoarrays of Individual Protein Molecules, Small (03 2012)
04/08/2012	5.00	Adam Garland, Lei Shen, Xiaoyang Zhu. Mobile Precursor State Mediated Protein Adsorption on Solid surfaces, Progress in Surface Science (09 2012)
TOTAL:	**3**	

Number of Manuscripts:

Books

Received	Paper
TOTAL:	

Patents Submitted

Patents Awarded

Awards

Fellow of the American Physical Society, 2011

Graduate Students

NAME	PERCENT SUPPORTED	Discipline
Adam Garland	0.50	
FTE Equivalent:	**0.50**	
Total Number:	**1**	

Names of Post Doctorates

NAME	PERCENT_SUPPORTED
Lei Shen	0.50
FTE Equivalent:	**0.50**
Total Number:	**1**

Names of Faculty Supported

NAME	PERCENT_SUPPORTED	National Academy Member
Xiaoyang Zhu	0.00	No
FTE Equivalent:	**0.00**	
Total Number:	**1**	

Names of Under Graduate students supported

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period:	0.00
The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:.....	0.00
The number of undergraduates funded by your agreement who graduated during this period and will continue to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:.....	0.00
Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):	0.00
Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for Education, Research and Engineering:	0.00
The number of undergraduates funded by your agreement who graduated during this period and intend to work for the Department of Defense	0.00
The number of undergraduates funded by your agreement who graduated during this period and will receive scholarships or fellowships for further studies in science, mathematics, engineering or technology fields:	0.00

Names of Personnel receiving masters degrees

NAME
Total Number:

Names of personnel receiving PHDs

NAME
Total Number:

Names of other research staff

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Sub Contractors (DD882)

Inventions (DD882)

Scientific Progress

This research program develops block copolymer thin films as model systems for understanding protein activity in the immobilized state and as effective technologies to achieve optimal protein activity on surfaces. Protein molecules immobilized on solid surfaces underpin a number of key technologies in bio-analysis, such as ELISA, biosensors, and protein microarrays for the large-scale screening and profiling in proteomics. A solid surface is intrinsically a foreign environment to protein molecules but little is known about the relationship between surface chemistry and protein conformation/activity in the immobilized state. The long-term goal of research program is to develop fundamental understanding of the essential structure-property relationship between the chemical structure of the surface and the activity of immobilized protein molecules. The proposed research uses block copolymer thin films to create chemical and geometrical patterns for the selective immobilization of protein molecules. Block copolymer thin films are known to be capable of generating chemically contrasting patterns with a high degree of order and uniformity. The characteristic dimensions of these patterns are tunable from a few to a few tens of nanometers, the exact length scale range of importance to protein functions. The chemical and geometrical properties of block copolymer thin films can be controlled by molecular design, methods of deposition, and post-deposition modification. Protein molecules are immobilized to particular domains on the nanoscopically ordered block-copolymer patterns. Enzymatic activity and protein refolding efficiency measured in the immobilized state can be correlated with the local chemical properties, such as hydrophilicity of the surrounding surface and dimensions of the patterns. A long-term outcome will be rationally designed surfaces to passively and actively control the activity of surface immobilized protein molecules, to enable the development and implementation of promising new technologies, e.g., protein microarrays and advanced biosensors, and to facilitate the improvement to existing and widely used ones, such as ELISA.
During the past funding period, the PI has developed a novel block-copolymer thin film, polystyrene-block-poly(2-hydroxyethyl methacrylate) (PS-b-PHEMA) diblock copolymers, as the model system for the investigation of a range of protein-surface interactions. The PS-b-PHEMA thin self-organizes well ordered patterns, such as hexagonally ordered vertical cylinders or vertically aligned lamellar. The PHEMA domain is partially hydrophilic, is non-fouling, and chemically/physically stable under aqueous solutions.

We study the dynamics of non-specific protein adsorption using nm – μm scale patterns involving hydrophobic domains in hydrophilic matrices. We report the discovery of a critical requirement on the sizes of the hydrophobic/adhesive pads for protein adsorption: the area of each adhesive pad must be more than two orders of magnitude larger than the footprint of a protein molecule before irreversible adsorption occurs. We attribute this to the minimal surface area sampled by a mobile protein molecule in a precursor state before irreversible adsorption occurs. Kinetic analysis based on the precursor model quantitatively accounts for the experimental observation and reveals that the distance sampled by the mobile precursor state before irreversible adsorption increases with the size of the protein molecule.

The interaction between a protein molecule and a surface is ubiquitous to a number of important technologies, such as bio-sensing, biomaterials, and nanomedicine. This process is also essential to complex biological functions, such as protein-cell surface interactions. Here we explore the application of fundamental concepts developed in the field of surface science to the understanding of protein-surface interactions. In particular, we focus on the role of mobile precursor states in the reversible and irreversible adsorption of protein molecules. We attempt to apply these simple concepts to the analysis of the kinetics and thermodynamics of protein-surface interactions. We conclude by discussing how one may take advantage of these simple concepts in designing and controlling protein-surface interactions for various bio-interface based technologies.

Protein molecules on solid surfaces are essential to a number of applications, such as biosensors, biomaterials, and drug delivery. In most approaches for protein immobilization, inter-molecule distances on the solid surface are not controlled and this may lead to aggregation and crowding. Here we show a simple approach to immobilize individual protein molecules in a well-ordered two-dimensional array using nano-patterns obtained from a polystyrene-block-poly(2-hydroxyethyl methacrylate) (PS-b-PHEMA) diblock copolymer thin film. This water stable and protein resistant polymer film contains hexagonally ordered PS cylindrical domains in a PHEMA matrix. We activate the PS domains by incorporating alkyne-functionalized PS and immobilize azide-tagged proteins specifically onto each PS domain using “Click” chemistry. The nanometer size of the PS domain dictates that each domain can accommodate no more than one protein molecule, as verified by atomic force microscopy imaging. Immunoassay shows that the amount of specifically bound antibody scales with the number density of individual protein molecules on the two-dimensional nanoarrays.

The aggregation of peptides into amyloid fibrils plays a crucial role in various neurodegenerative diseases. While it has been generally recognized that fibril formation in vivo can be greatly assisted or accelerated by molecular surfaces, such as cell membranes or macromolecule surfaces, little is known about the mechanism of surface mediated fibrillation. Here we study the dynamics of fibril formation of Alzheimer’s amyloid-ß peptide (Aß42) at the liquid-solid interface of chemically functionalized and nano-patterned surfaces. Using single molecule fluorescent tracking and atomic force microscopy imaging, we show that weakly adsorbed peptides with two-dimensional diffusivity are critical precursors to fibril growth on surfaces. This surface mediated growth mechanism is inhibited when the diffusion constant of the majority of adsorbed peptides drops below 1 μm2/s. This discovery on surface mediate fibrillation opens the door to new strategies in disrupting or inhibiting fibril growth via interfacial control.

Technology Transfer

Controlling Protein Conformation and Activities on Block-Copolymer Nanopatterns

PI: Xiaoyang Zhu; Postdoc/student: Lei Shen, Adam Garland
Department of Chemistry & Biochemistry
University of Texas at Austin

Long-term Scientific Goal

- To understand and control the activity of surface immobilized protein molecules.

Project-specific Goal

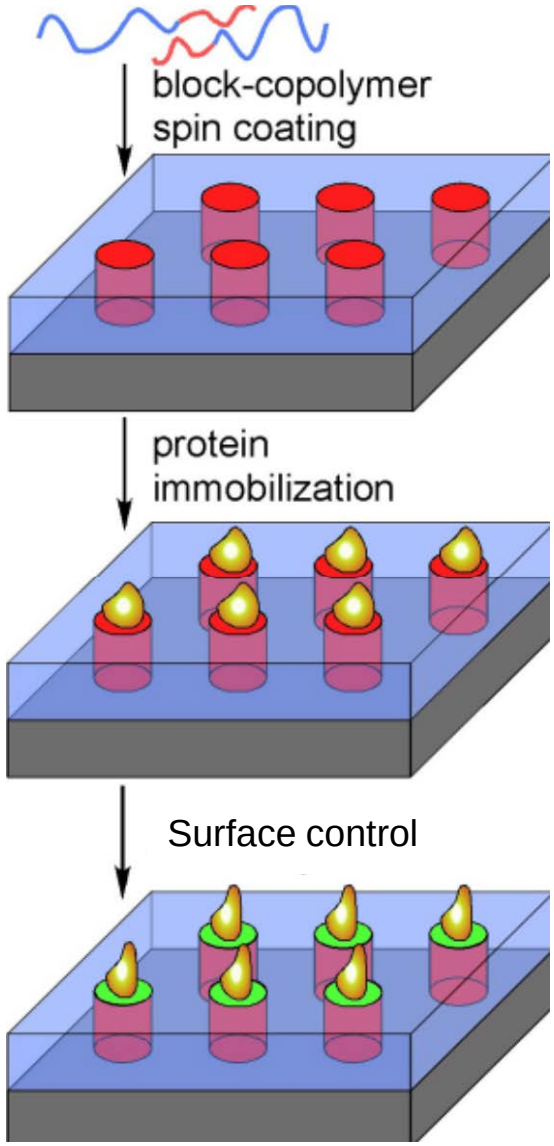
- To develop block copolymer thin films as model systems for understanding protein adsorption and interaction on surfaces
- To develop nano-scale patterned polymer surfaces for optimal protein activity in the immobilized state.

Specific experimental approaches:

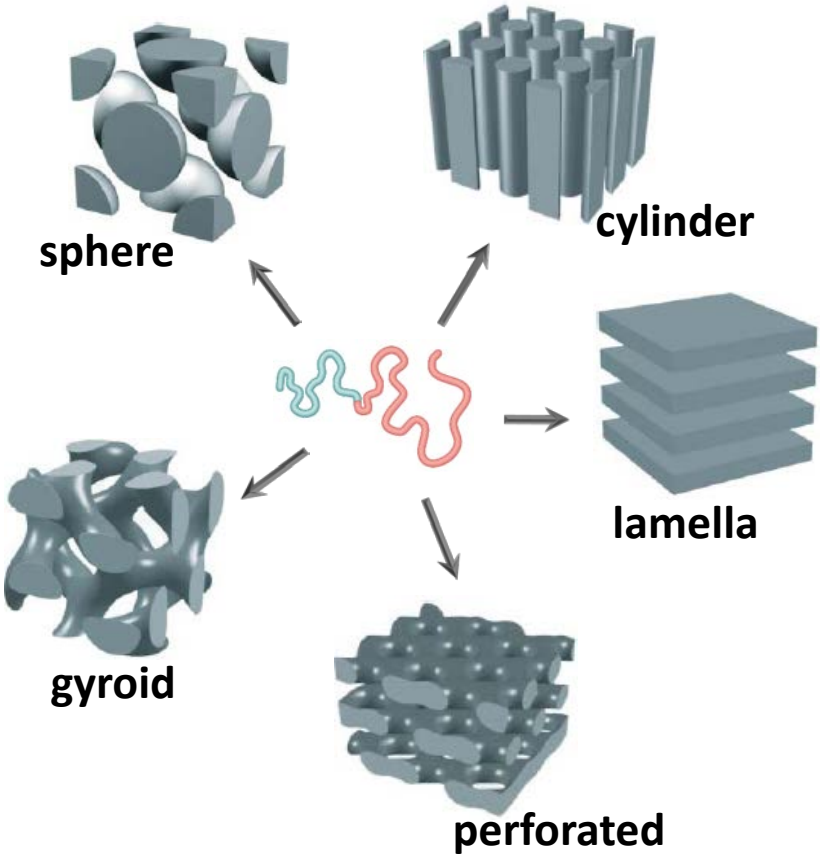
• To use block copolymer thin films in the vertical cylinder phase to create ordered patterns for protein immobilization.

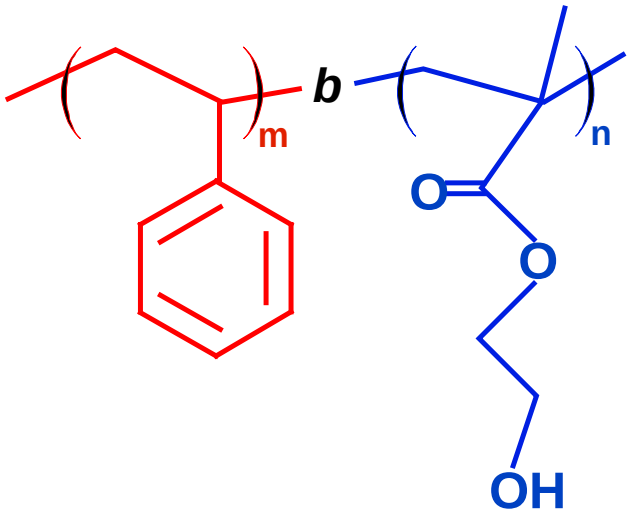
• To immobilize protein molecules and form nanoarrays with individual protein molecules.

• To systematically control the local chemical environment and thus the conformation/activity of immobilized protein molecules.



Polymer surface

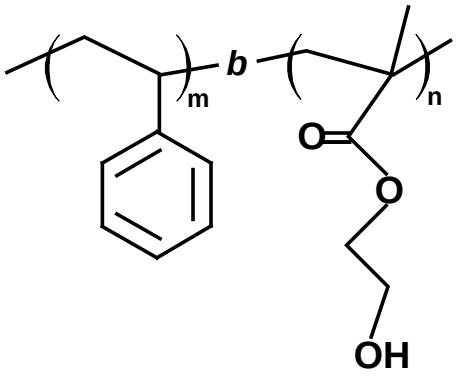




PS-*b*-PHEMA

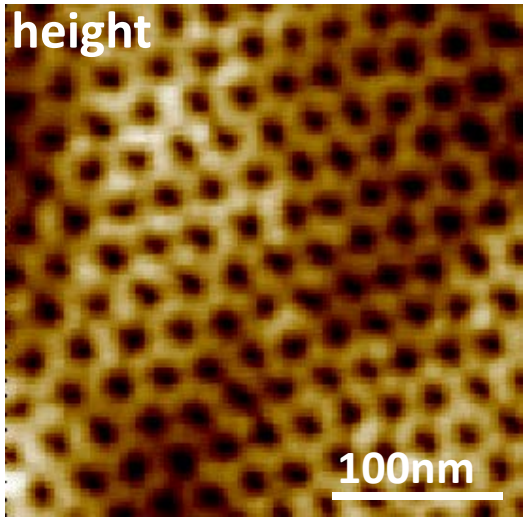
***hydrophobic*/*hydrophilic* surfaces**

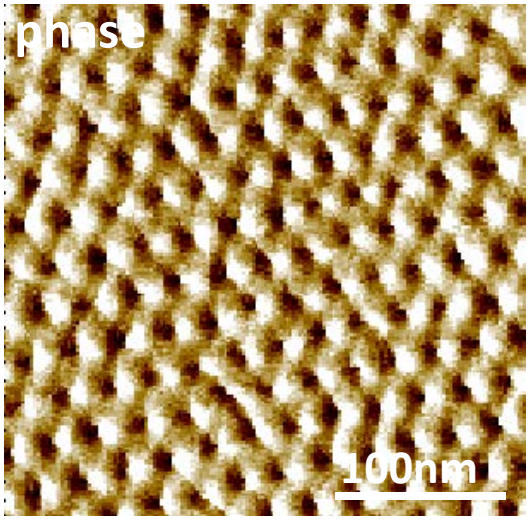
Nanoscorpic Polymer Pattern



PS_{200}-*b*-$PHEMA_{50}$

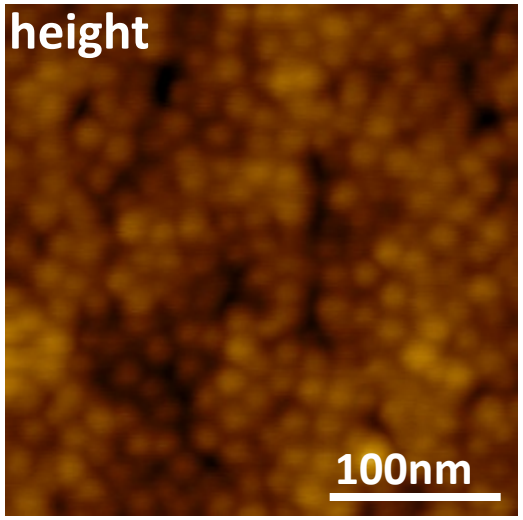
$M_w/M_n = 1.08$

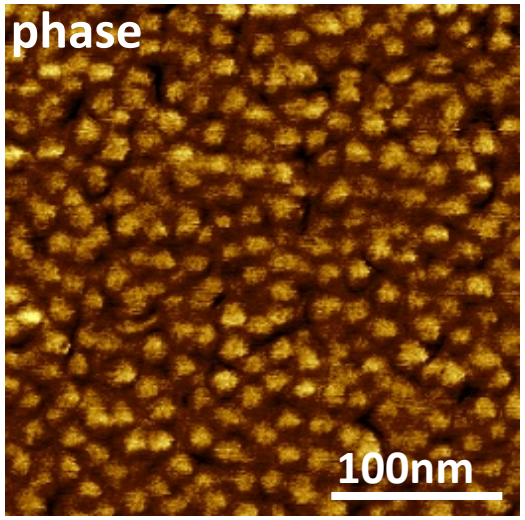




PS_{60}-*b*-$PHEMA_{150}$

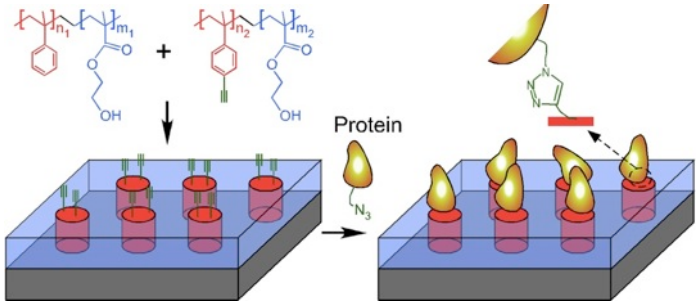
$M_w/M_n = 1.10$



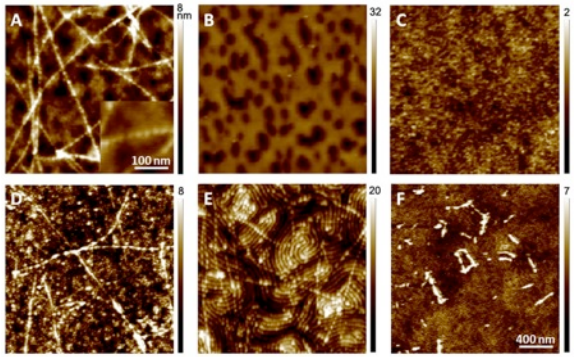


Highlights of Research Accomplishments

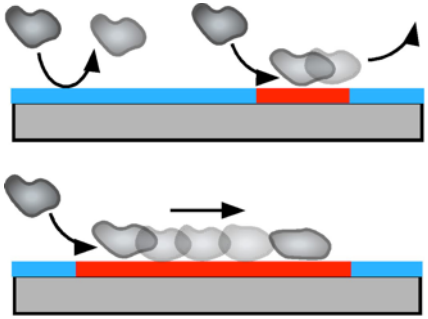
- Discovered a critical requirement on the sizes of the hydrophobic/adhesive pads for protein adsorption and the presence of mobile precursor states.
- Developed polymer thin film and surface chemistry for the fabrication of nanoarrays of individual protein molecules (with Prof. Chris Bielawski).
- Use polymer nanopatterns to establish the fundamental mechanism for peptide fibril formation.



Small 8 (2012) DOI: 10.1002/smll.201200673



JACS (2012) reviewed positively. In revision



Langmuir 27 (2011) 7059–7064.

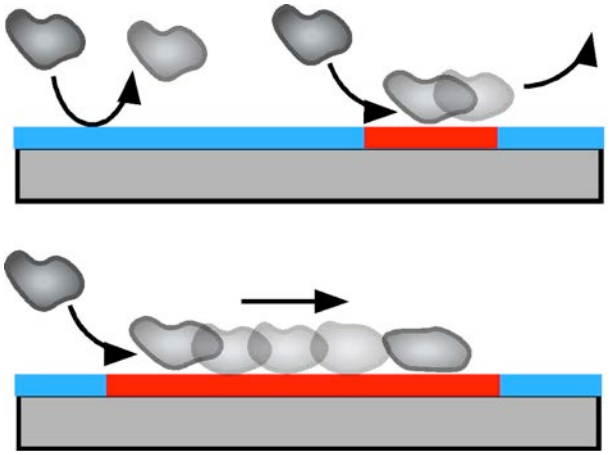
L. Shen, Athena Guo, X.-Y. Zhu, “Tween surfactants: adsorption, self-organization, and protein resistance,” Surf. Sci. 605 (2011) 494–499.

A. Garland, L. Shen, X.-Y. Zhu, “Mobile Precursor State Mediated Protein Adsorption on Solid surfaces,” Prog. Surf. Sci. 87 (2012) 1-22

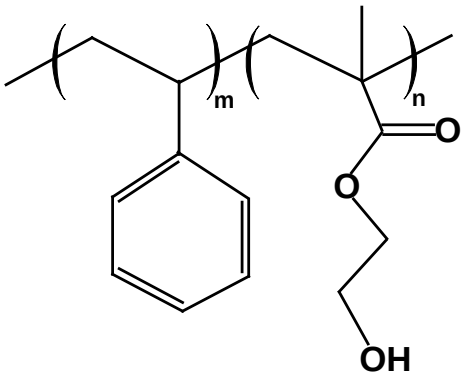
Highlight 1: Evidence of a mobile precursor state in non-specific protein adsorption

• Block copolymer thin films in the vertical cylinder phase.

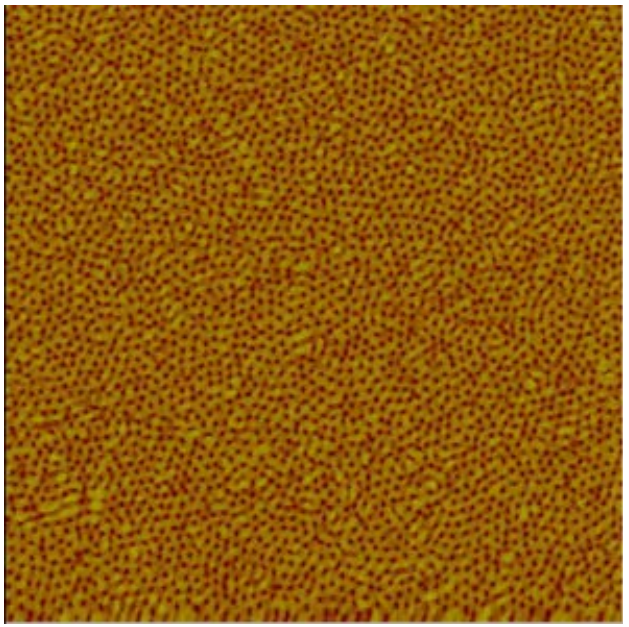
• *How big does the "sticky" pad needs to be?*



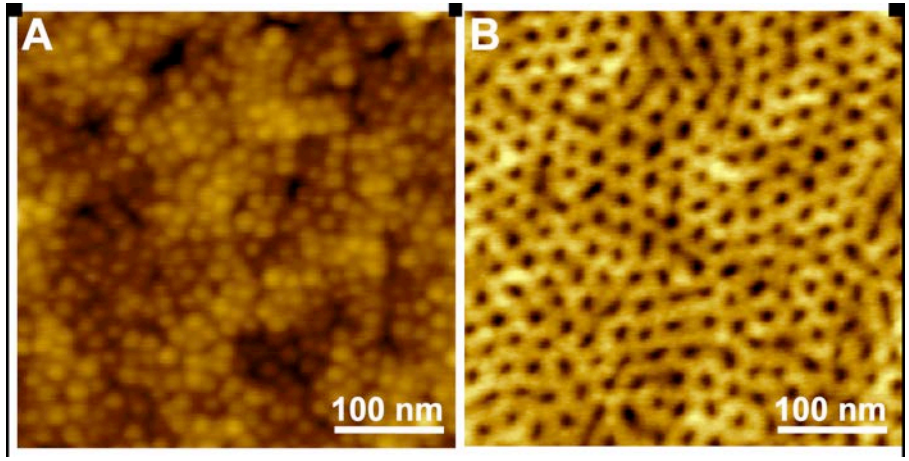
The model: polystyrene-*block*-poly(2-hydroxyethyl methacrylate): PS-b-PHEMA



Hydrophobic Hydrophilic



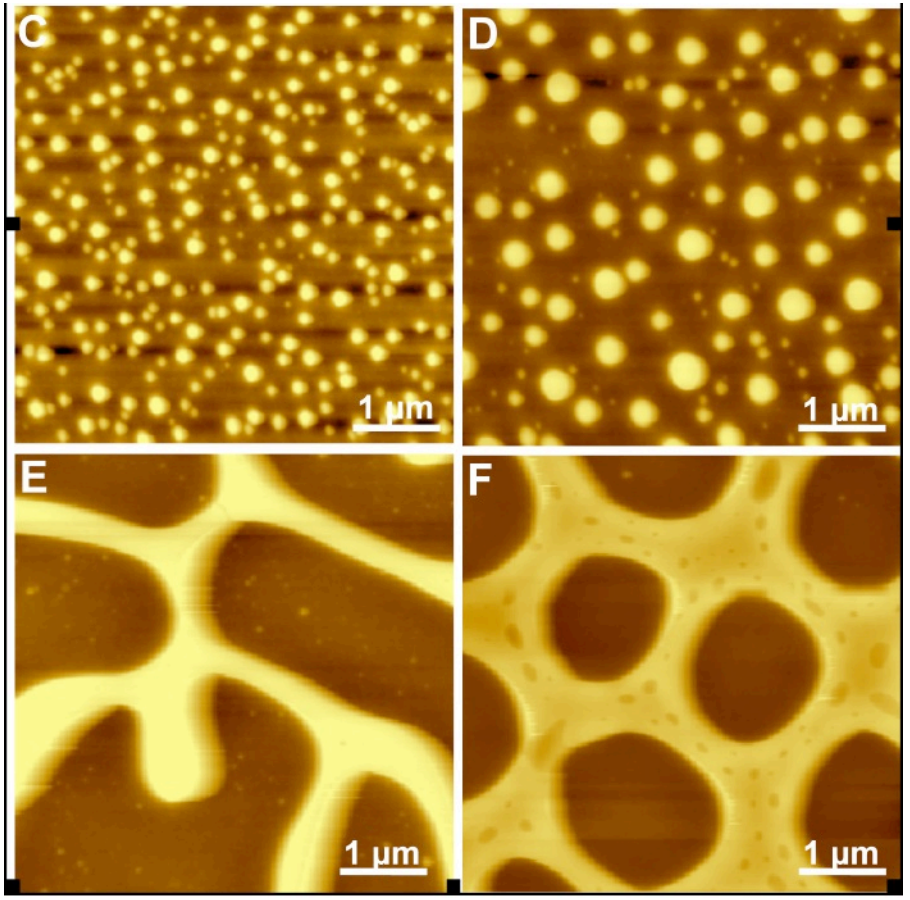
Tunable size of “sticky” pads (the PS domains)



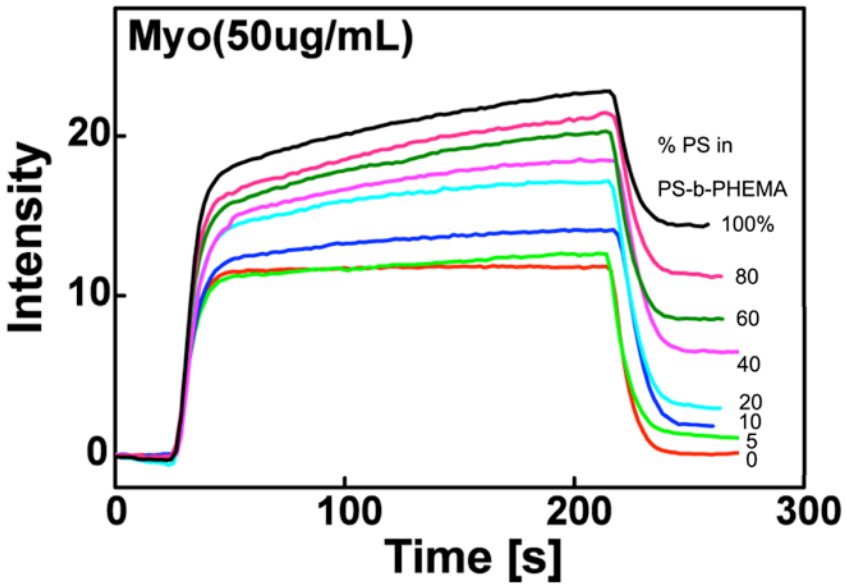
A) PS_{60}-b-$PHEMA_{150}$,
B) PS_{200}-b-$PHEMA_{50}$

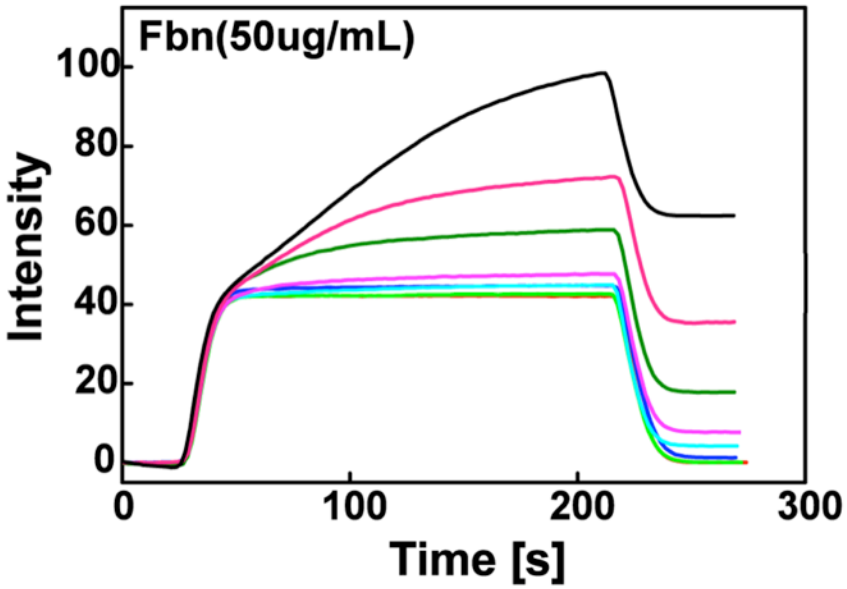
PS_{60}-b-$PHEMA_{150}$/PS mixtures with different weight ratio (φ) of PS homopolymer:

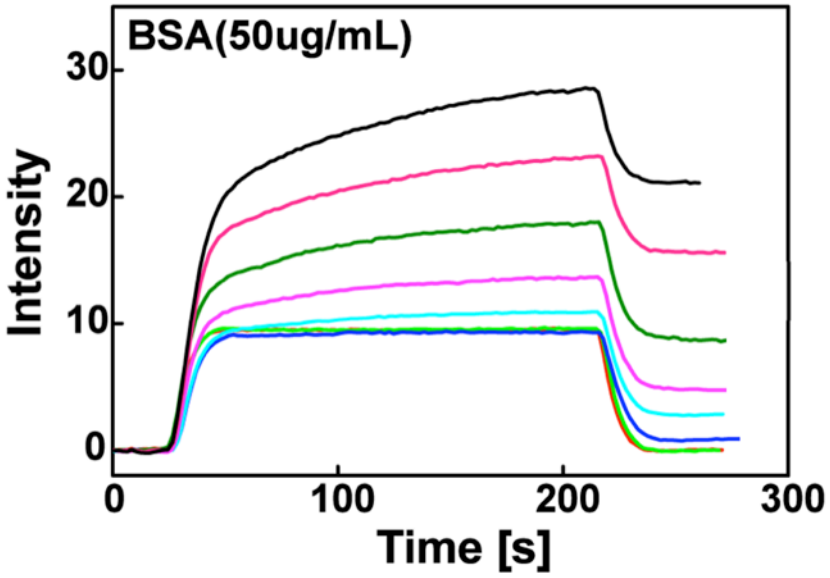
C) 0.1, D) 0.2, E) 0.4 and F) 0.6.



Quantifying Protein adsorption on the nanopatterns by surface plasmon resonance (SPR) spectroscopy

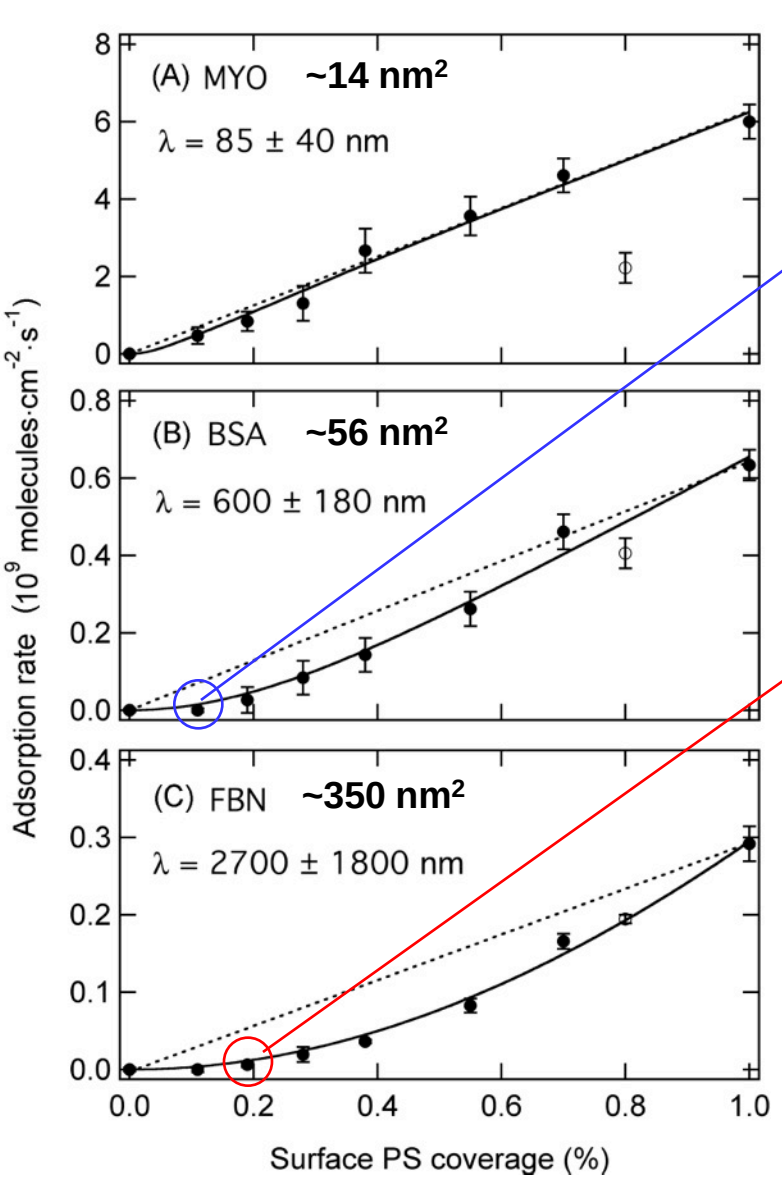


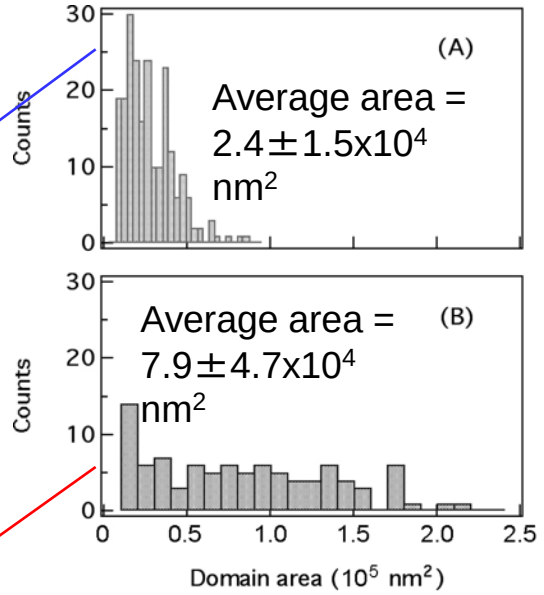


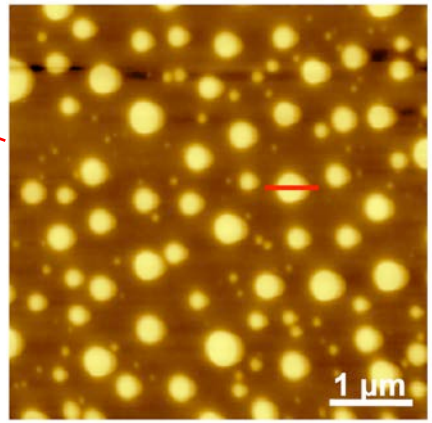


Three different protein sizes: Myoglobin (MYO, $4 \times 3.5 \times 2$ nm^3), Bovine serum albumin (BSA, $8 \times 7 \times 4$ nm^3) Fibrinogen (FBN, $50 \times 7 \times 7$ nm^3)

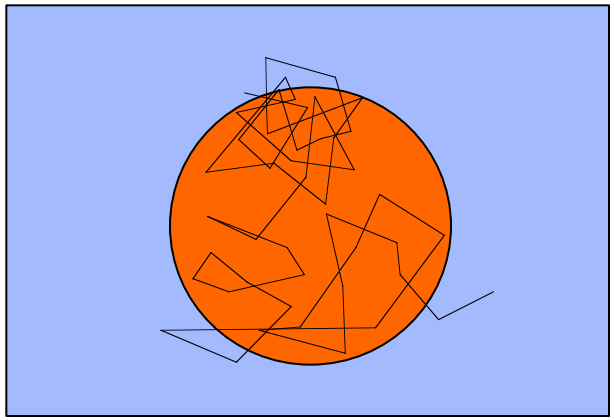
Size dependent protein adsorption: the need for large stick pads!







Kinetic model:



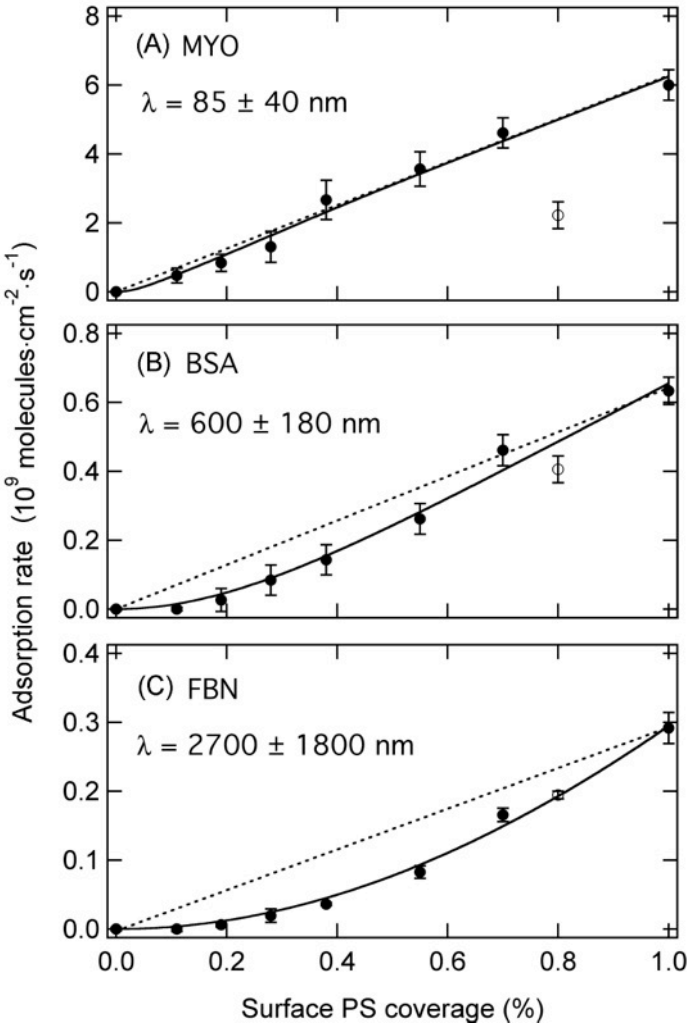
Random walk approximation

$$M + \theta_{PS} \underset{k_d}{\overset{k_{a'}}{\square}} \theta' \xrightarrow{k_a} \theta$$

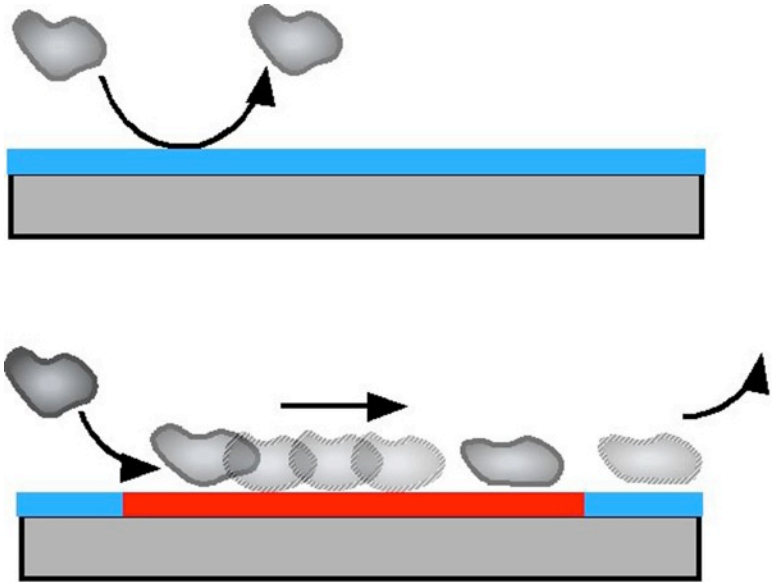
$$k_d = k_o \cdot p;\ k_a = k_o \cdot (1\text{-}p).$$

$$p = \int_R^{\infty} \sqrt{\frac{2}{\pi}} \frac{1}{\lambda} \exp\left(-\frac{x^2}{\lambda^2}\right) dx$$

$$r_a = \frac{d\theta}{dt} = k_{a'} \cdot [M] \cdot \theta_{PS} \cdot (1 - p)$$



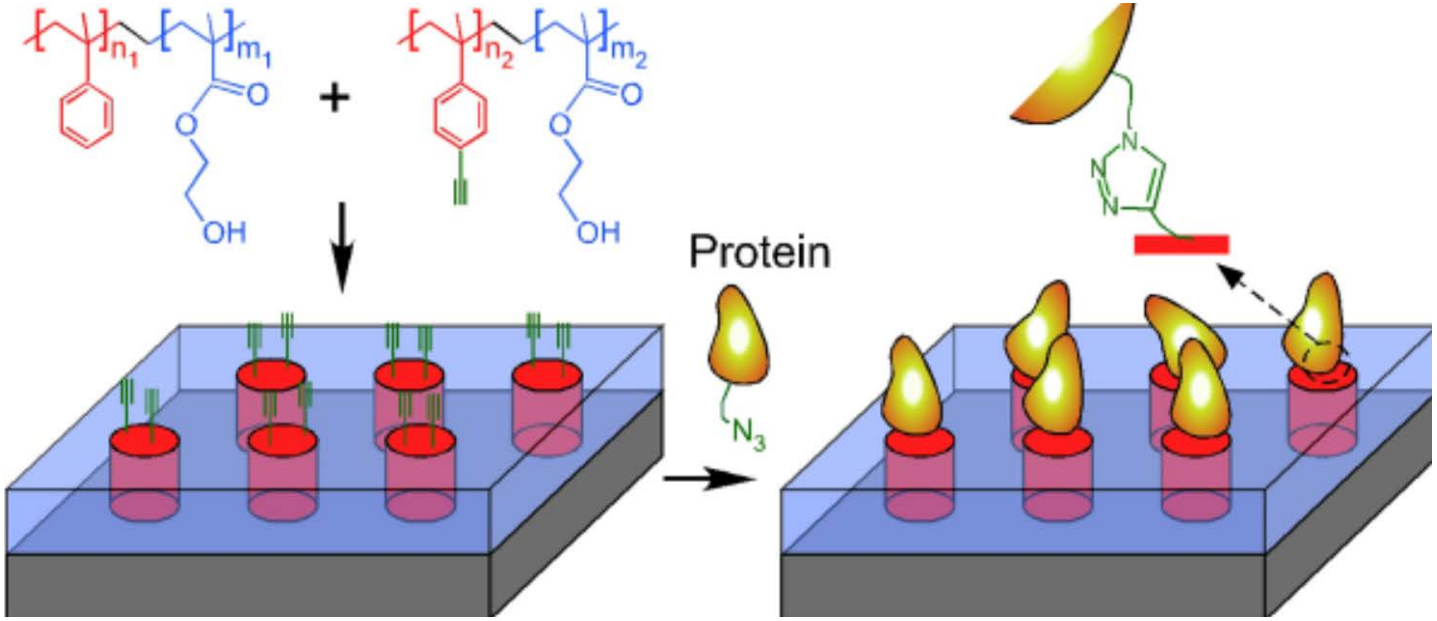
Summary 1: A nanoscopic view of protein adsorption



- **Protein adsorption requires sticky pads of critical sizes ≥ $10^{2\text{-}3}$ times large than the footprint of a protein molecule.**

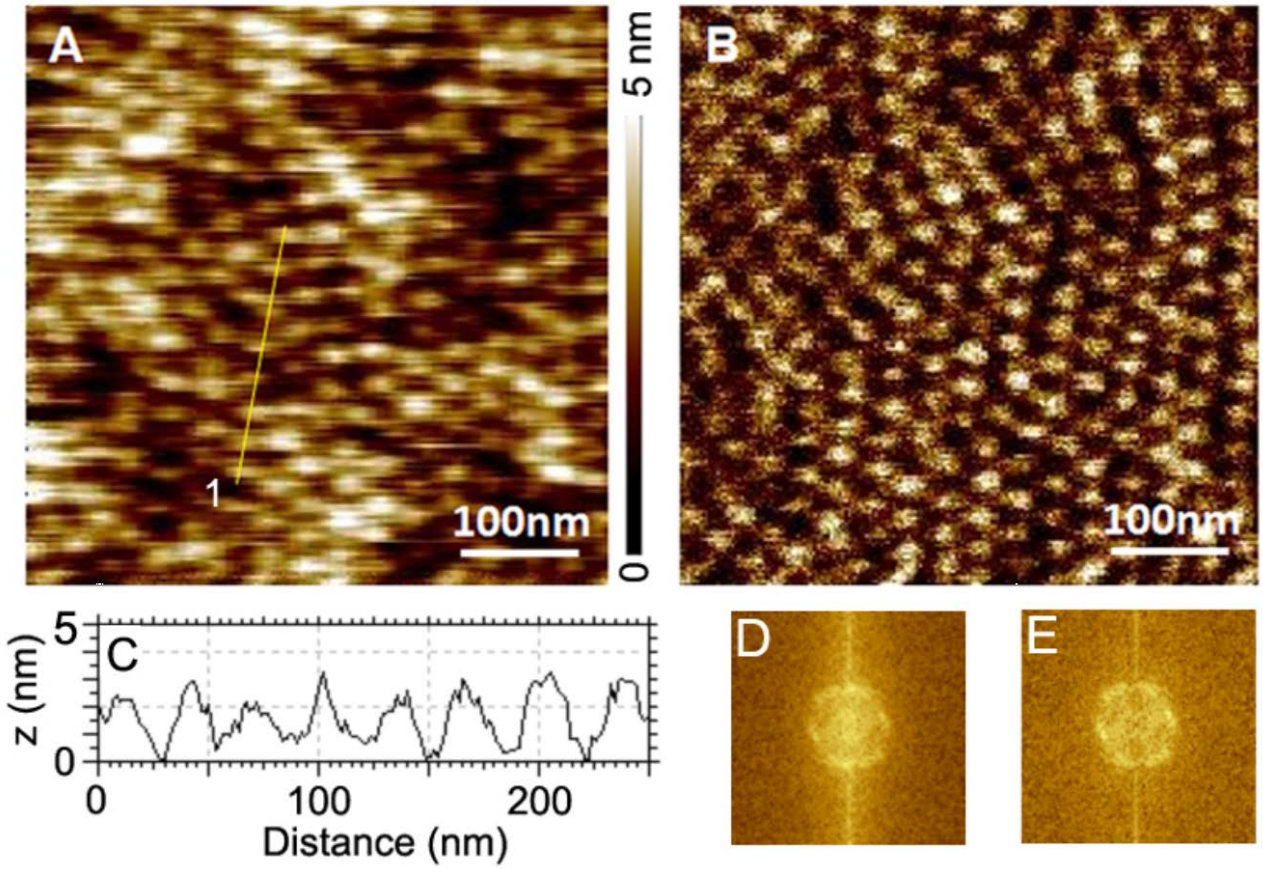
- **There is a mobile precursor state in which the protein molecule re-organizes to maximize interaction with the hydrophobic surface.**

Highlight 2: Polymer nanopattern & click chemistry for protein immobilization



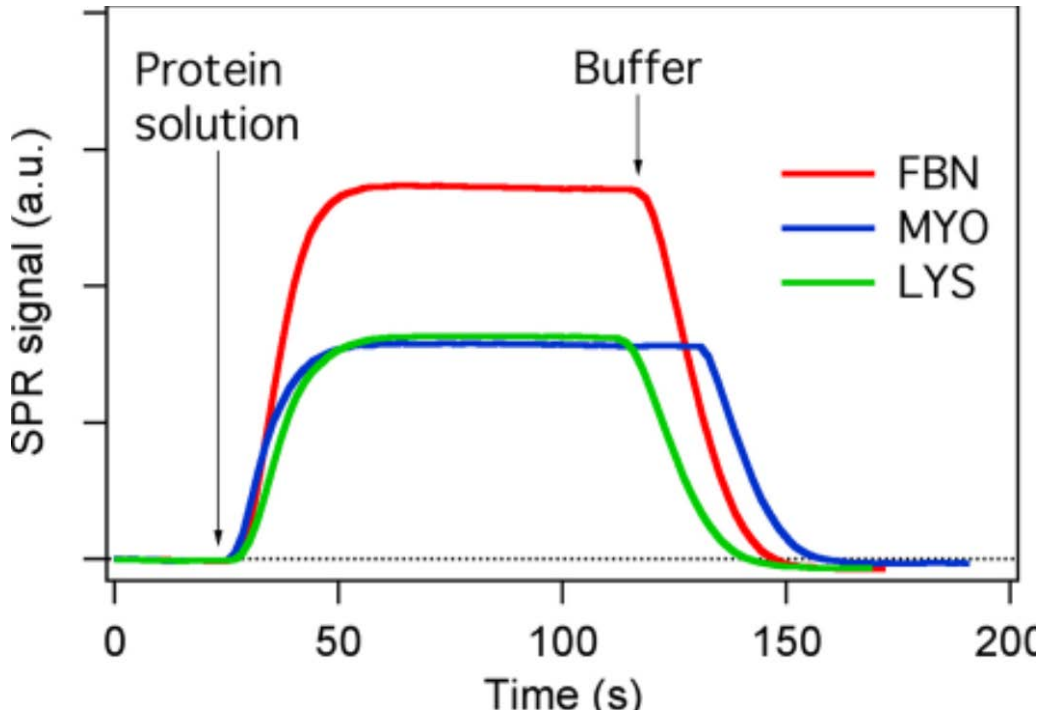
Schematic illustration of the generation of PS-*b*-PHEMA block-copolymer thin film with PS cylinders (red) in the PHEMA (blue) matrix. The PS domains present alkyne functionality for the specific immobilization of azide-tagged protein molecules via click chemistry.

The nano template from block-copolymers



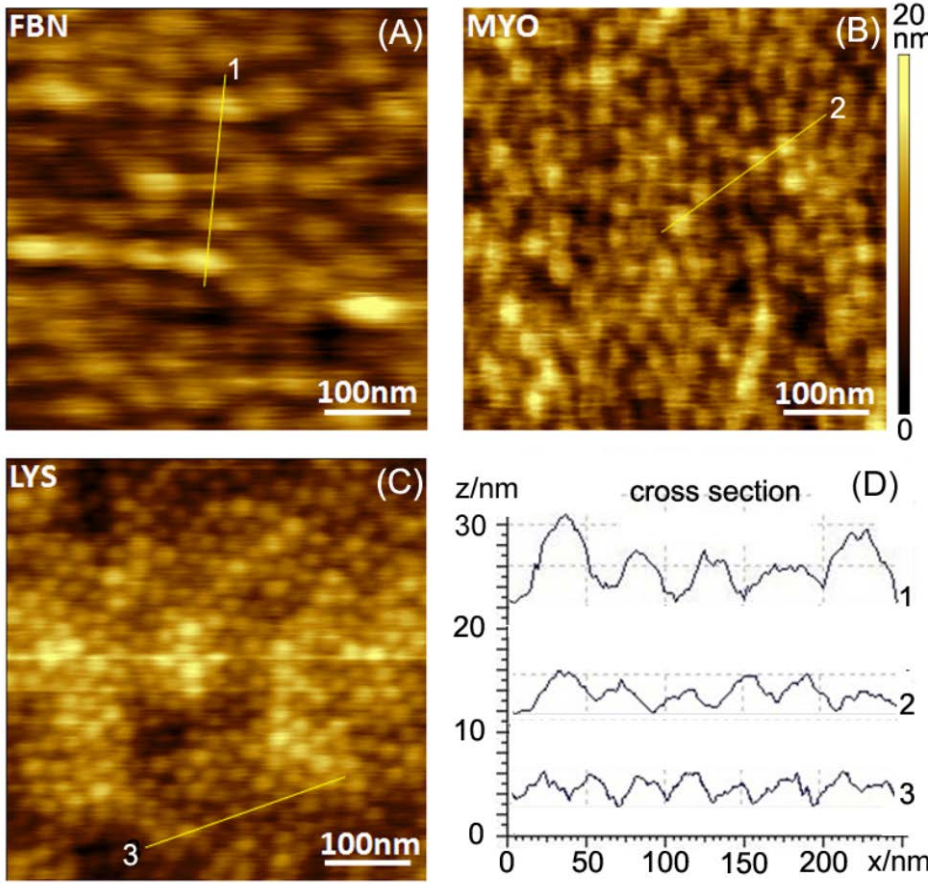
AFM images for PS-*b*-PHEMA thin film in water: A) topography, B) phase, and C) cross sectional profile of line 1 in the topographical image. Panels D & E show the Fourier transform of topographical and phase images, respectively.

The Absence of Nonspecific Protein adsorption on the nanopatterns by surface plasmon resonance (SPR)

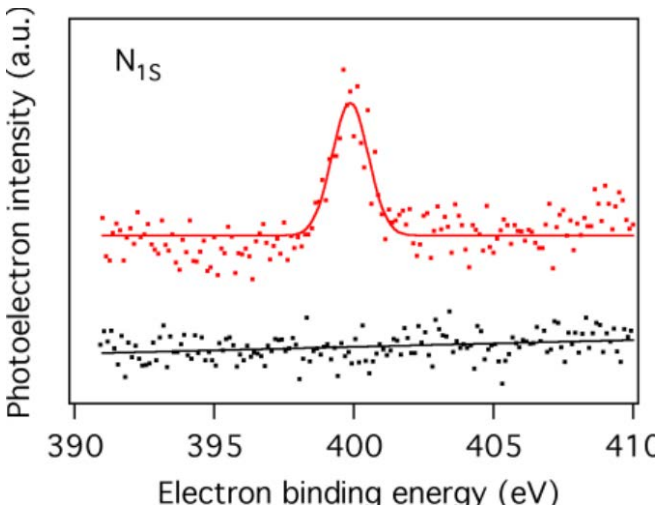


Surface plasmon resonance responses of the PS-*b*-PHEMA block-co-polymer coated sensor surface upon exposure to protein solutions (red: FBN, blue: MYO, and green: LYS) and washing buffers. Note the signal returns to the baseline after the injection of washing buffer in each case.

The specific immobilization of individual protein molecules on the block-copolymer pattern

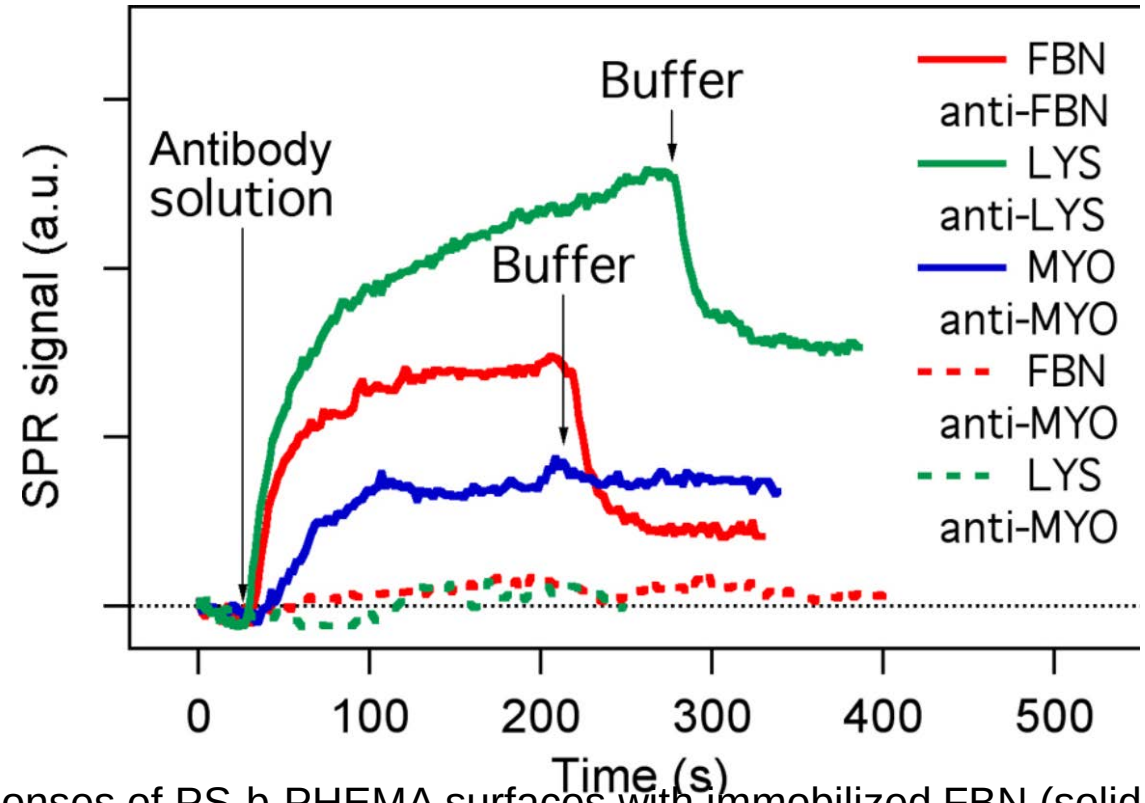


AFM height images taken under aqueous solution of (A) FBN, (B) MYO, and (C) LYO immobilized on the PS-*b*-PHEMA block-copolymer thin film surface. Panel (D) shows three cross sectional profiles (height vs. lateral distance, offset for clarity) of the three images.



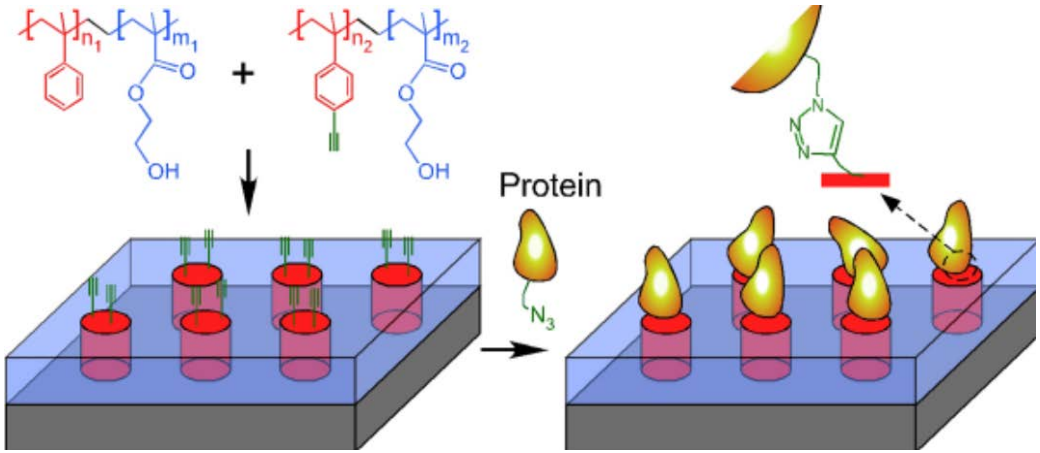
X-ray photoelectron spectra (XPS) for PS-*b*-PHEMA thin film samples that have been immersed in the azide-FBN solution for six hours with (red) and without (black) the Cu(I) catalyst. The presence of immobilized protein molecules is verified by the N_{1s} signal in the former.

Antibody recognition of immobilized proteins on the block-copolymer nanoarray



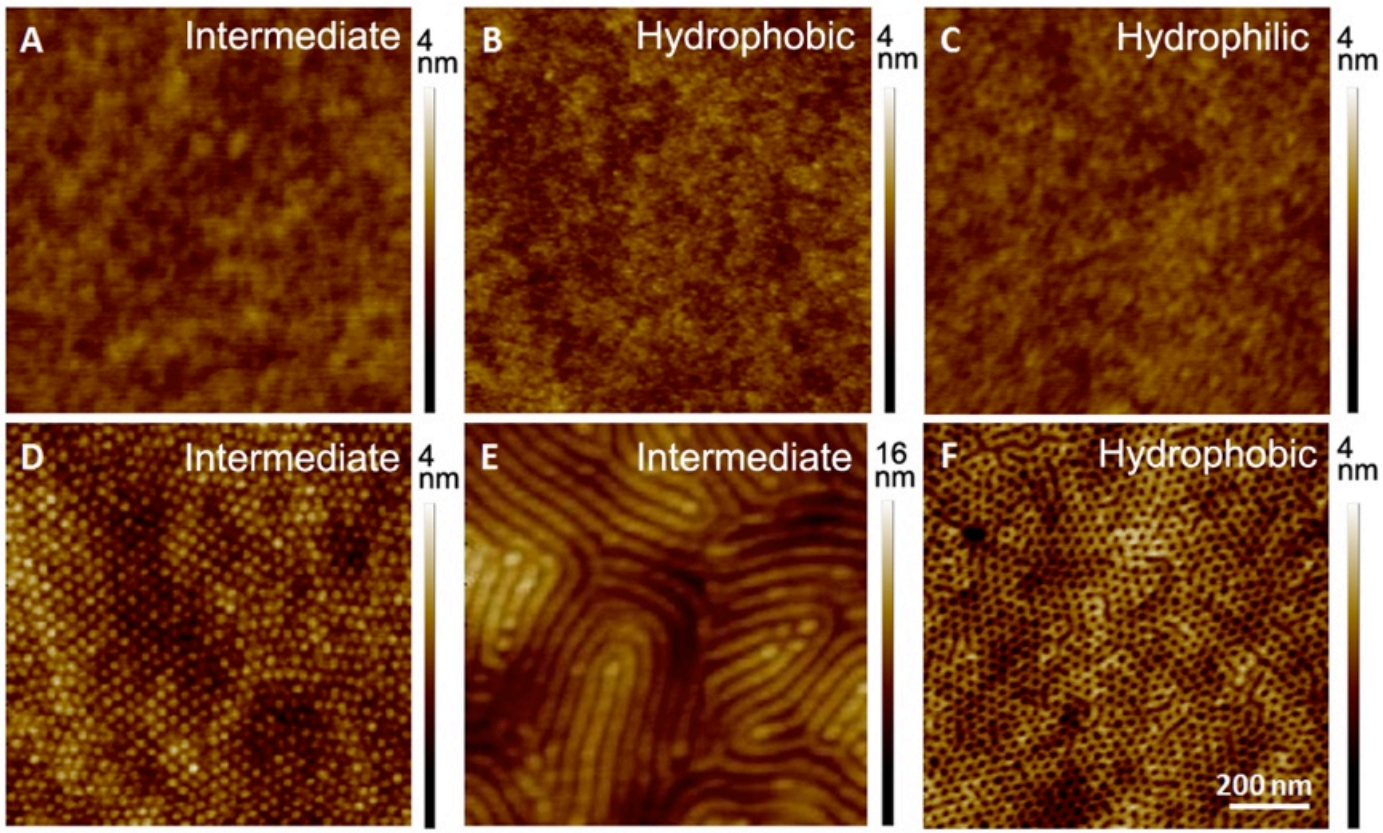
SPR responses of PS-b-PHEMA surfaces with immobilized FBN (solid red), MYO (solid blue), and LYS (solid green) proteins with exposure to corresponding antibody solutions: anti-FBN, anti-MYO, and anti-LYS, respectively. Also shown are control experiments with the FBN (red-dashed) and LYO (green dashed) surface exposed to the anti-MYO antibody solution. Note that the refractive index of the anti-MYO solution is similar to that of the washing buffer.

Summary 2: protein nanoarrys



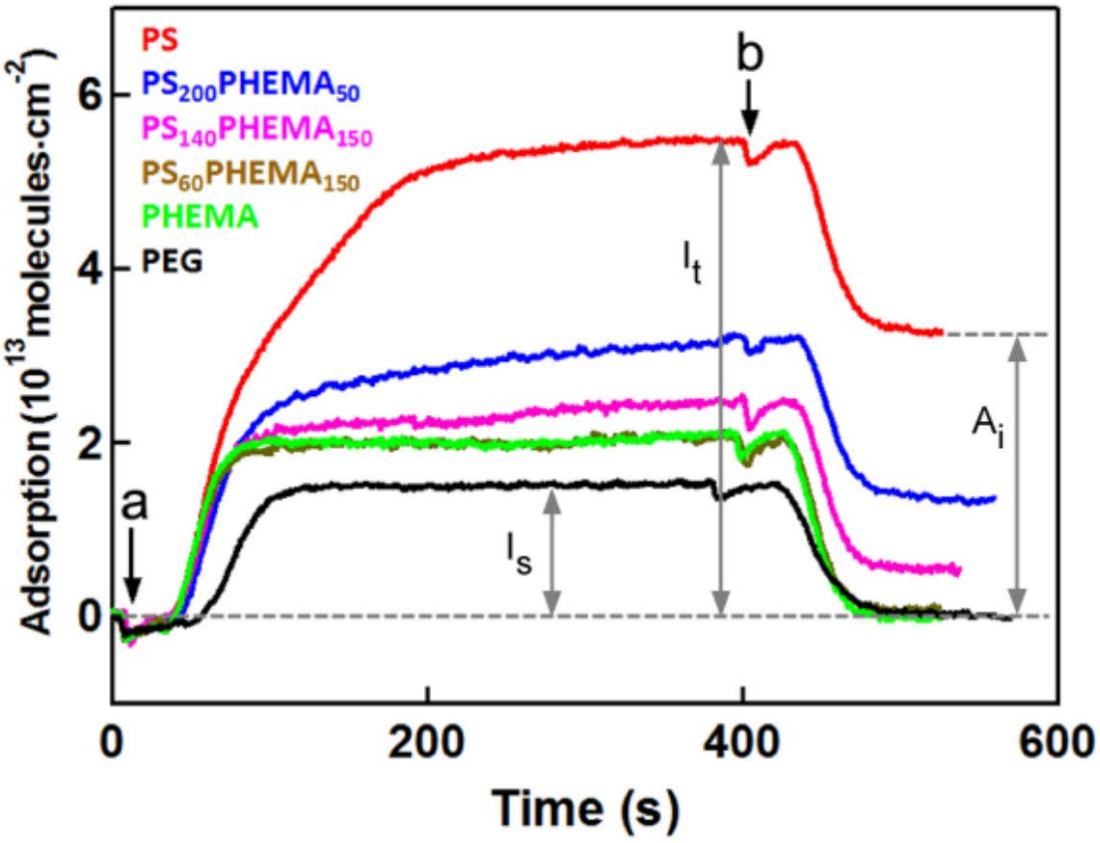
- Two-dimensional nanoarrays of individual protein molecules on an ordered nano-pattern of a PS-*b*-PHEMA diblock copolymer thin film.
- The polymer surface repulsive to nonspecific protein and stable in an aqueous environment.
- Specific immobilization of azide-tagged protein molecules only to the alkyne-functionalized PS cylinder domain
- Specific binding of antibody molecules to the nanoarray.
- Wide ranging applications, such as biosensing and assaying, biomaterials, and mechanistic cell biochemistry studies.

Nano-patterned polymer thin films for the investigation of peptide fibril growth



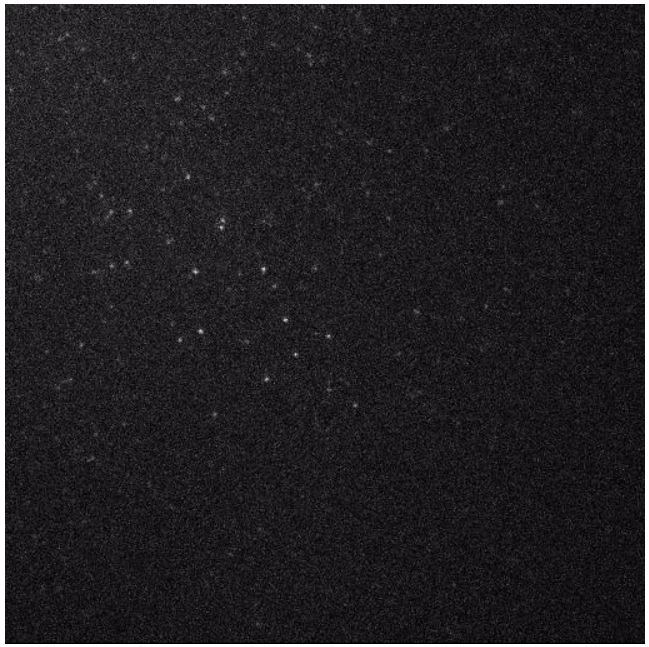
AFM images of thin films of A) PHEMA, B) PS, C) PEG, D) PS_{60}-*b*-$PHEMA_{150}$, E) PS_{140}-*b*-$PHEMA_{150}$, and F) PS_{200}-*b*-$PHEMA_{50}$. The diameters of PS domains (bright) in B or PHEMA domains (dark) in D are ~20 nm. The width of each PS (bright) or PHEMA (dark) domain in C is ~ 50 nm.

Quantifying weakly and strongly adsorbed peptides on the polymer surfaces

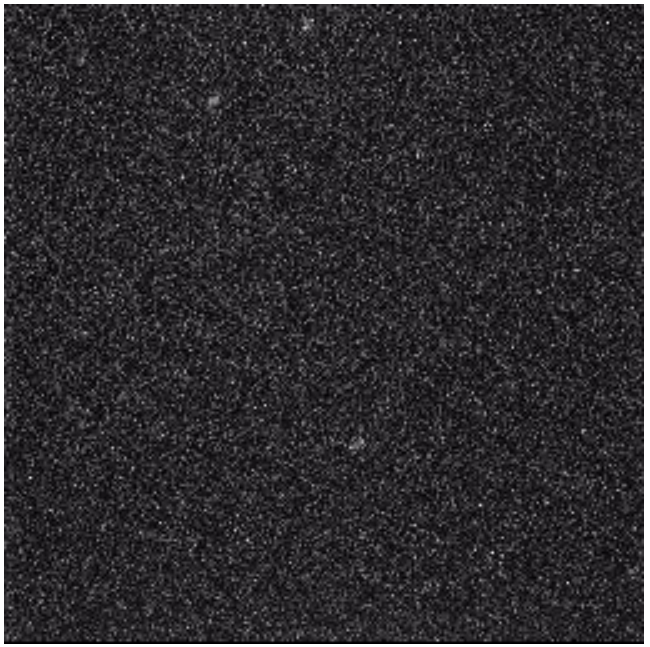


The SPR responses for Aβ42 peptide (1 μM in PBS) adsorption on PEG, PHEMA, PS_{60}-*b*-$PHEMA_{150}$, PS_{140}-*b*-$PHEMA_{150}$, PS_{200}-*b*-$PHEMA_{50}$ and PS surfaces.

Mobility of Aβ42 on Polymer Surfaces

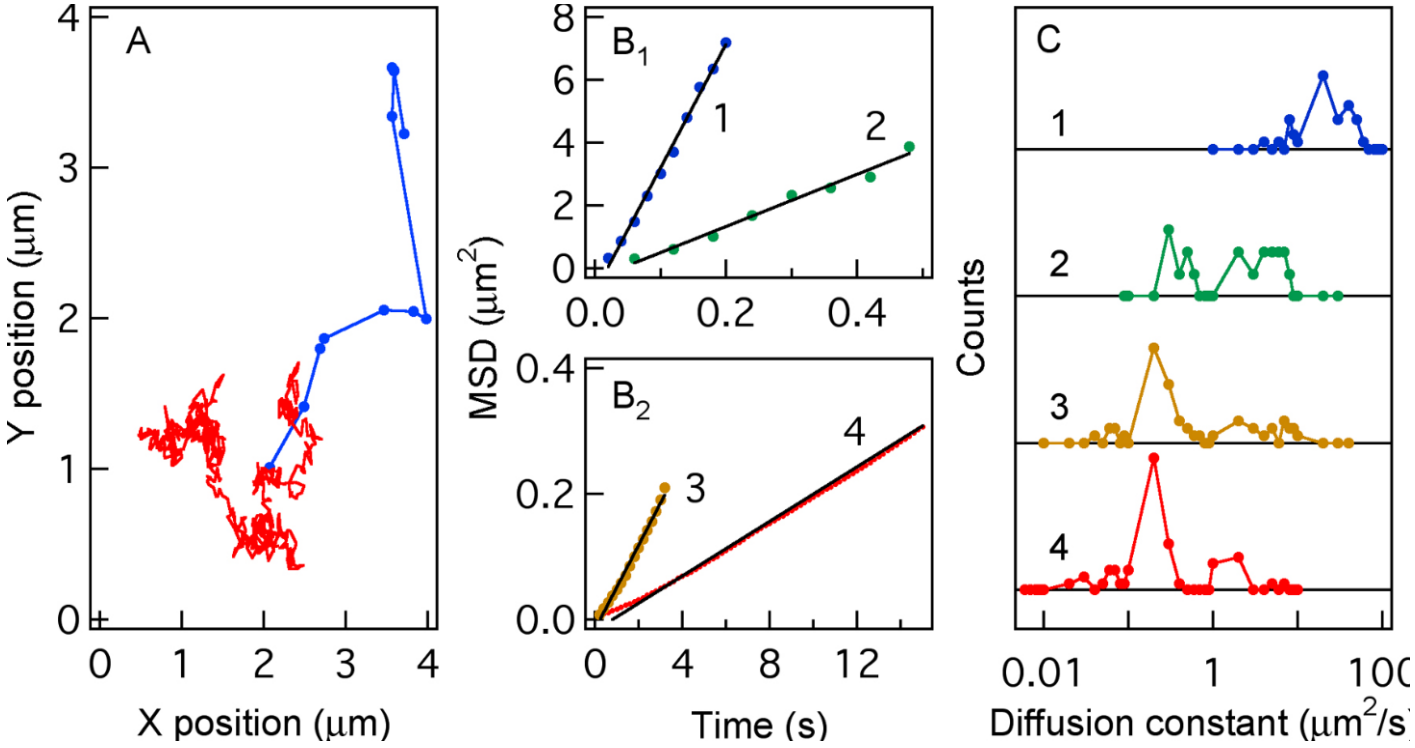


PS



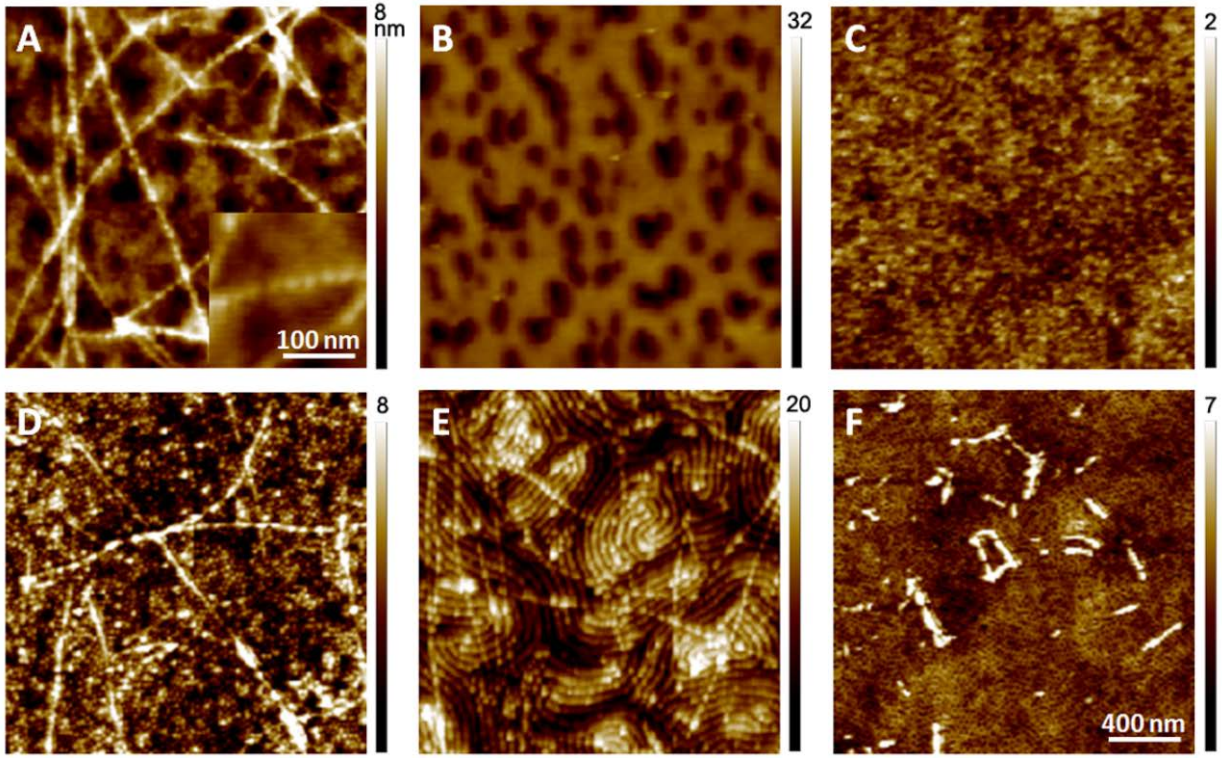
PHEMA

Single molecule fluorescence tracking of Aβ42 peptide on polymer surfaces



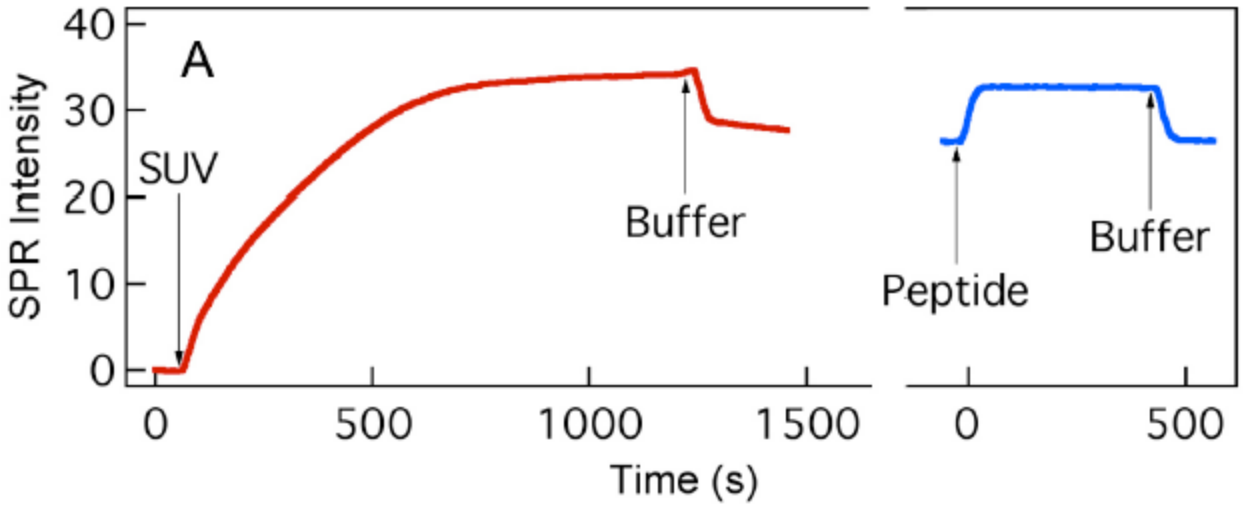
A) Single molecule trajectories of Aβ42 on PHEMA (blue, 12 successive steps, 20 ms per step) and PS (red, 601 successive steps, 200 ms per step) surfaces; B) Mean squared displacement (MSD) as a function of time for sample single molecule trajectories of Aβ42 on 1) PHEMA, 2) PS_{140}-b-$PHEMA_{150}$, 3) PS_{200}-b-$PHEMA_{50}$ and 4) PS surfaces. Note that the data are presented on two different scales (B_1 & B_2) for clarity. Solid lines are linear fits to MSD(t) = 4*D*t, where *D* is the two-dimensional diffusion constant. C) Histograms of the diffusion coefficients of Aβ42 monomers on four polymer films: 1) PHEMA, 2) PS_{140}-b-PHEMA150, 3) PS_{200}-b-$PHEMA_{50}$ and 4) PS. Each data set is offset for clarity and the solid horizontal line correspond to zero counts in each case. Note the logarithmic scale for the X-axis.

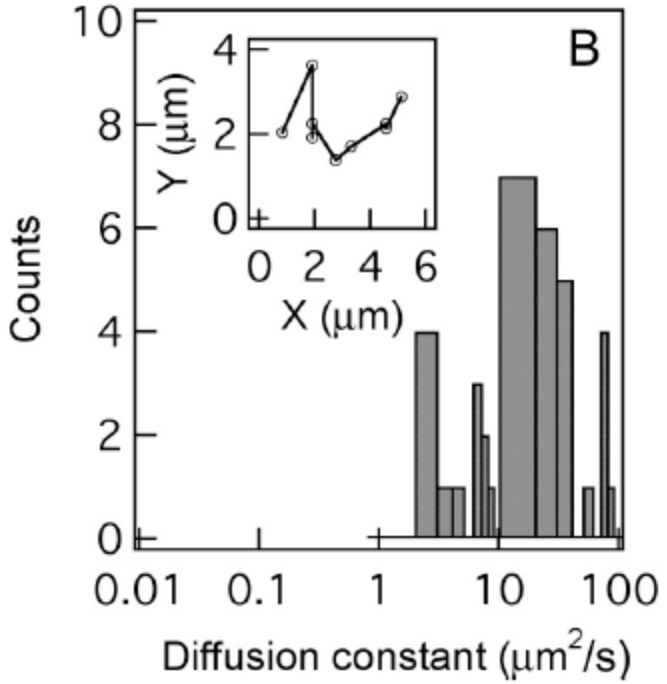
Aβ42 fibril growth on polymer nanopatterns

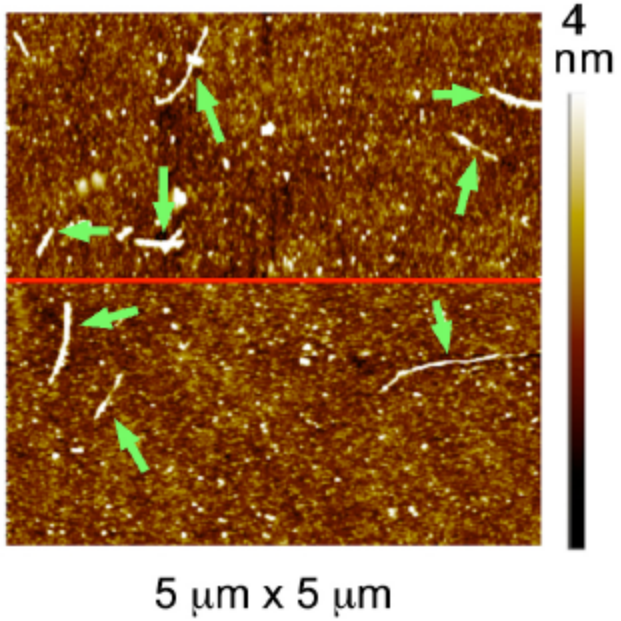


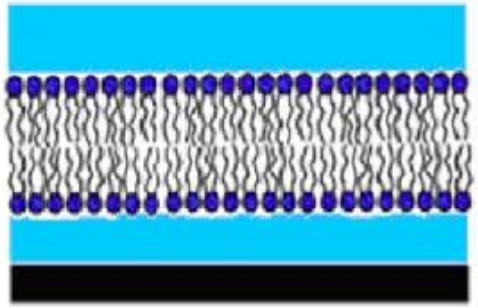
AFM images taken in the air for the polymer this films thin films (see Fig. 1) after they have been incubated in Aβ42 peptide solution (1 μM in PBS) at 37°C for 18 hours. A) PHEMA, B) PS, C) PEG, D) PS_{60}-*b*-$PHEMA_{150}$, E) PS_{140}-*b*-$PHEMA_{150}$, and F) PS_{200}-*b*-$PHEMA_{50}$. The inset in panel (A) is a zoomed-in image showing the helical structure of the fibril. The width of each fibril is ~20 nm. The scale bar is 400 nm (for all panels). The pseudo color scales (height) are in units of nm.

Fibrillization on lipid bilayer

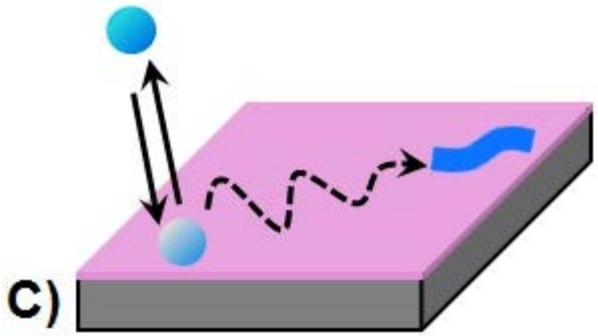


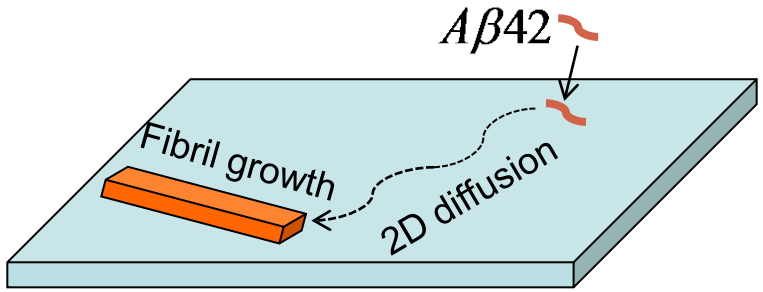






Summary 3: Surface assisted fibril formation mediated by mobile precusors



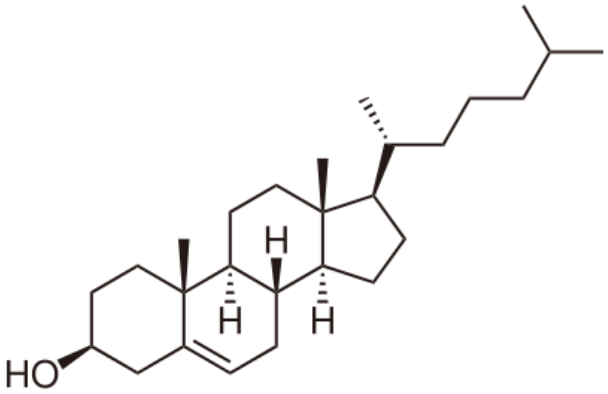


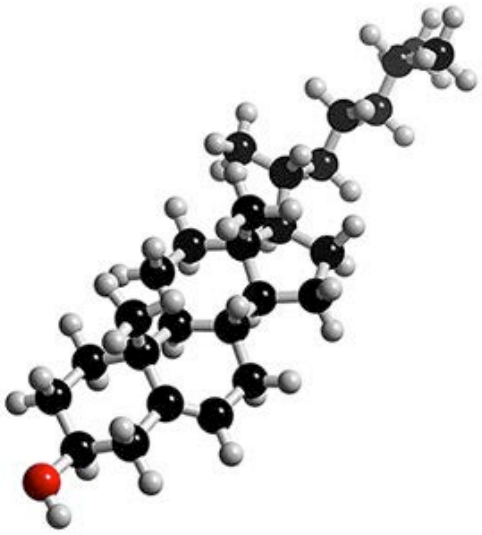
Intermediate hydrophobicity

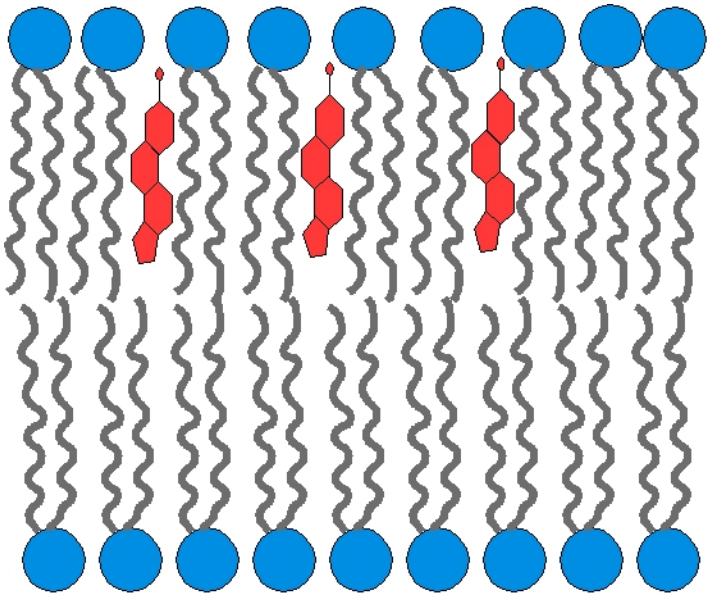
- Dynamics of surface mediated fibril formation of Alzheimer's amyloid-β peptide (Aβ42) on polymers and supported lipid bilayers.
- Single molecule fluorescent tracking and atomic force microscopy imaging show that weakly adsorbed peptides with two-dimensional diffusivity are critical precursors to fibril growth on surfaces.
- The surface mediated mechanism is inhibited when the diffusion constant of the majority of adsorbed peptides is below 1 $\mu m^2/s$.

Lesson 2 from Nature: cholesterol

The magic molecule



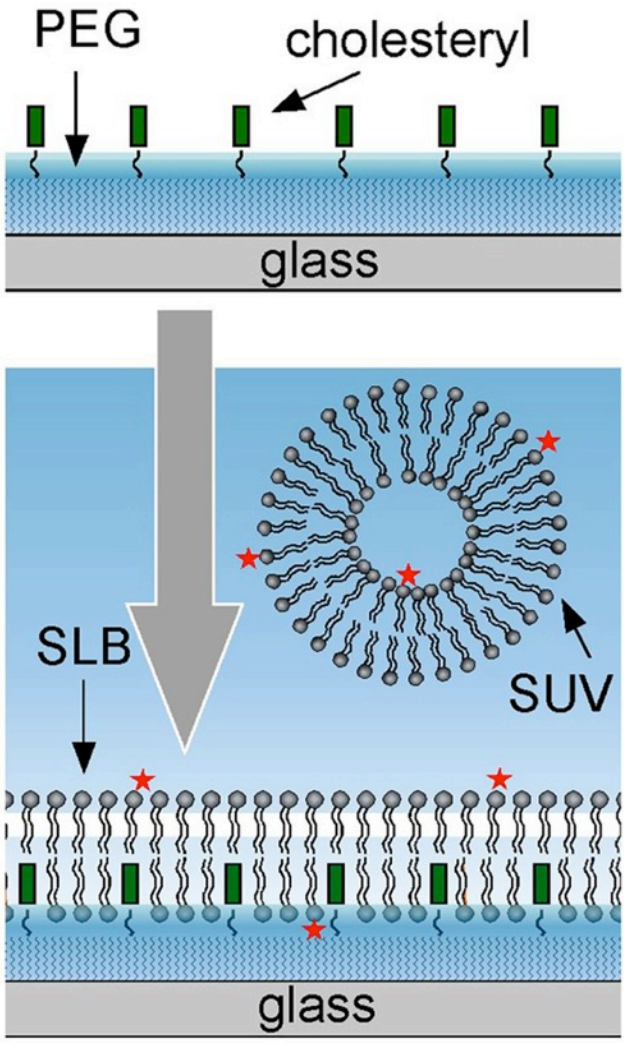


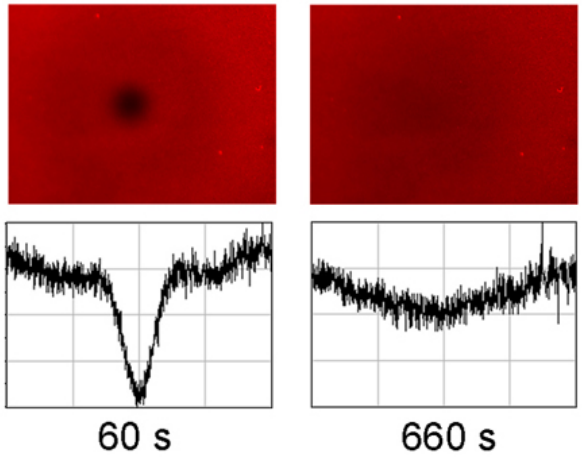


- **Increase lipid packing density by up to 40%**
- **From liquid-disordered to liquid-ordered phase**
- **Increase membrane rigidity (bending & expansion modulus)**
- **But cholesterol tend to cluster - Rafts!**

***Annu. Rev. Biophys. Biomol. Struct.* 33, 269 (2004)**
***Biophys. J.* 90, 1639 (2006)**

Make SLBs air-stable from "bottom up"



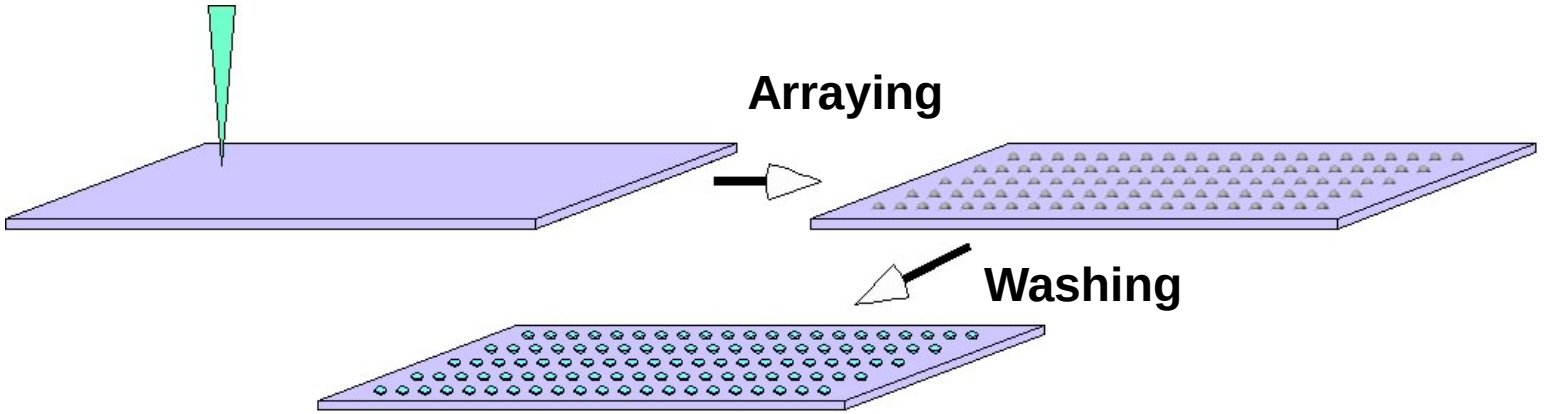


Fluorescence recovery after photobleaching (FRAP)

The supported lipid bilayer becomes air-stable at a critical cholesterol density of 0.3/nm^2, i.e., cholesterol:lipid = 1:6 to 1:8 (bottom leaflet).

J. Am. Chem. Soc. 2008, 130. 6267

Ongoing research: developing polymer curshions for cell membrane-mimicking microarrays



Proteomics

- GPCRs
- Ion channels
- mAbs
- Other membrane proteins…

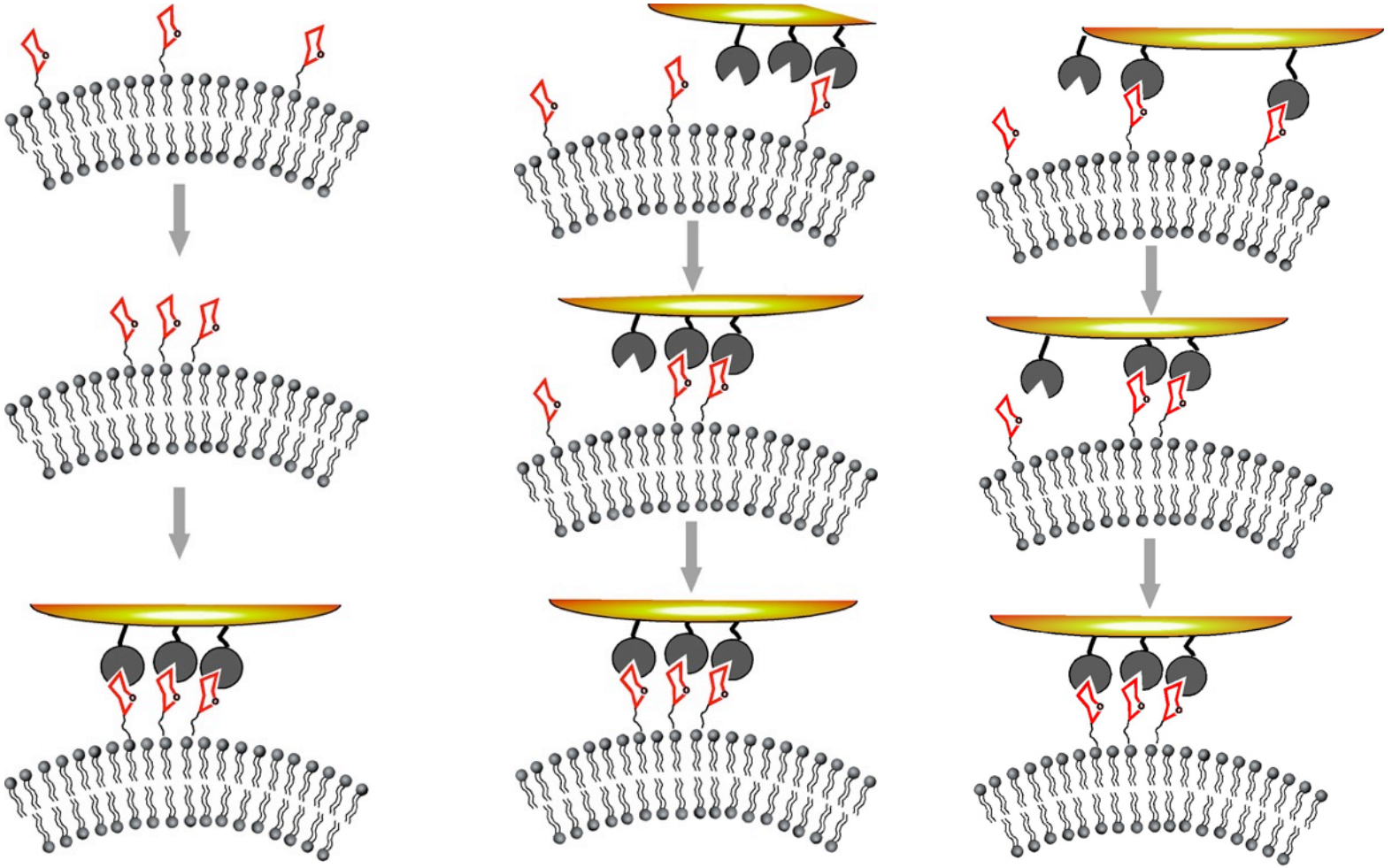
Glycomics

- Pathogen recognition
- Cell growth
- Cell-cell communication, etc.

Nanomedicine

- Drug delivery
- Drugs & therapy
- In vivo imaging…

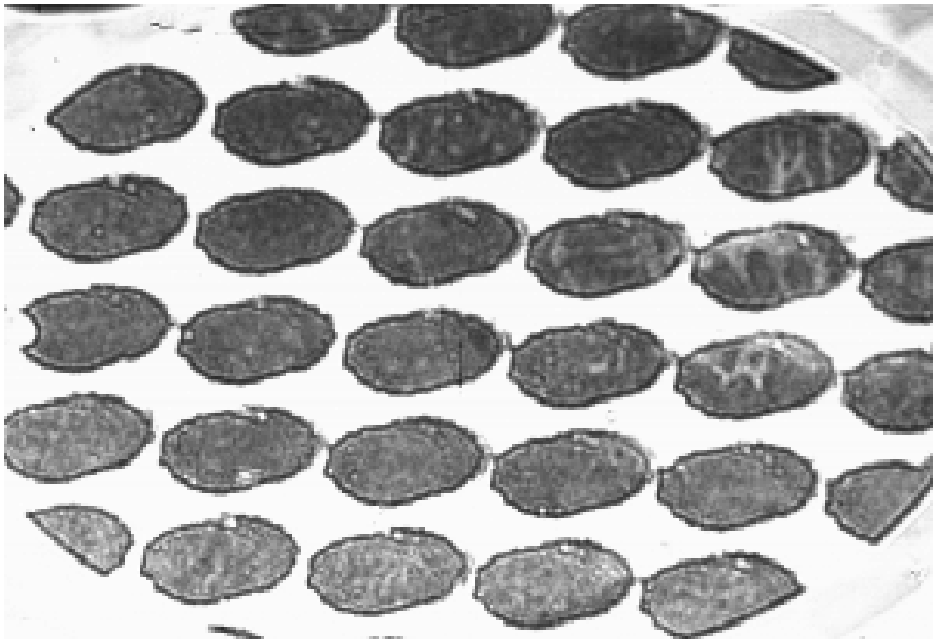
Fluidity in multivalent interactions



Pre-clustering - “sweet spot”

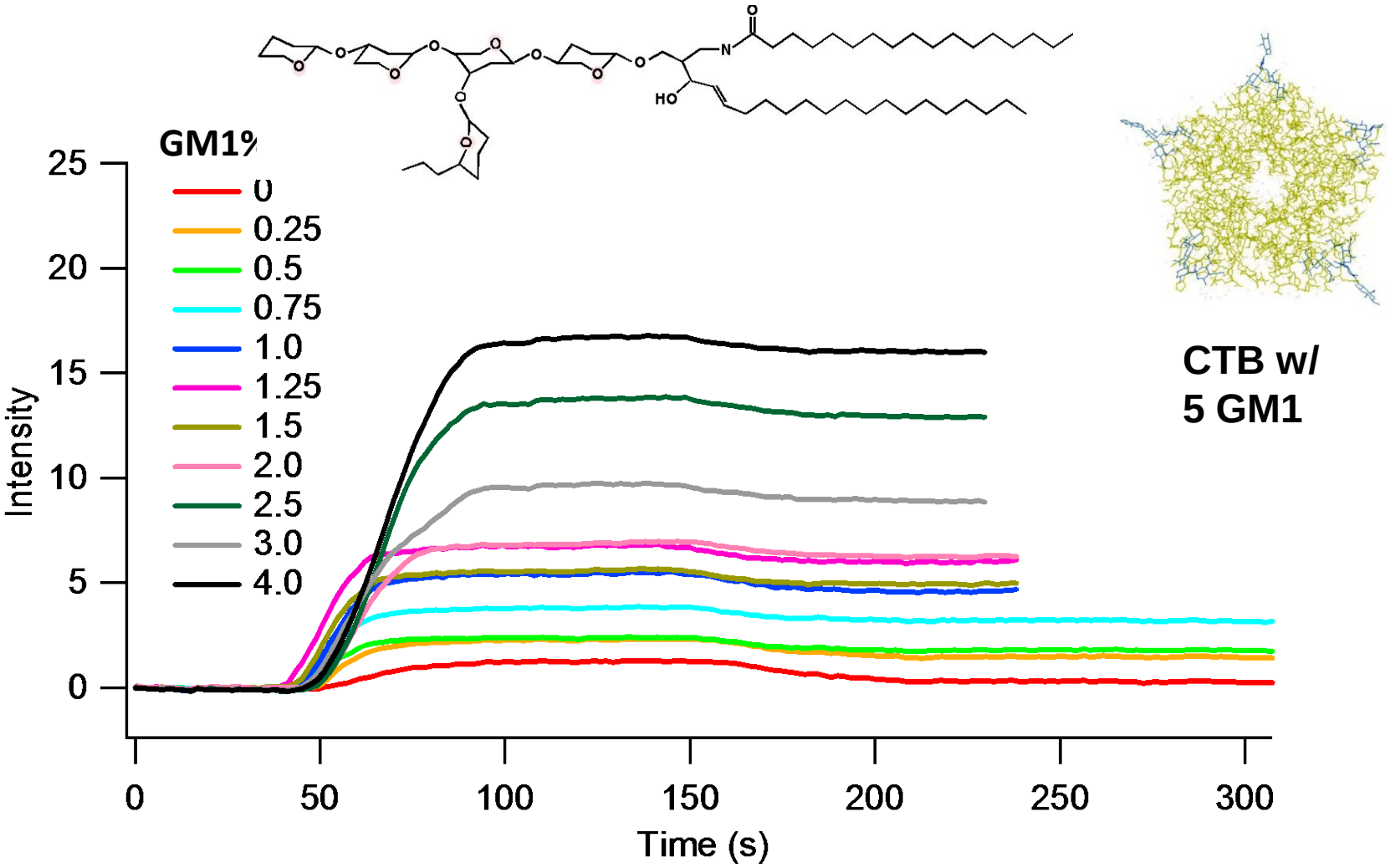
Dynamic-clustering

Label free lipid bilayer arrays with SPR

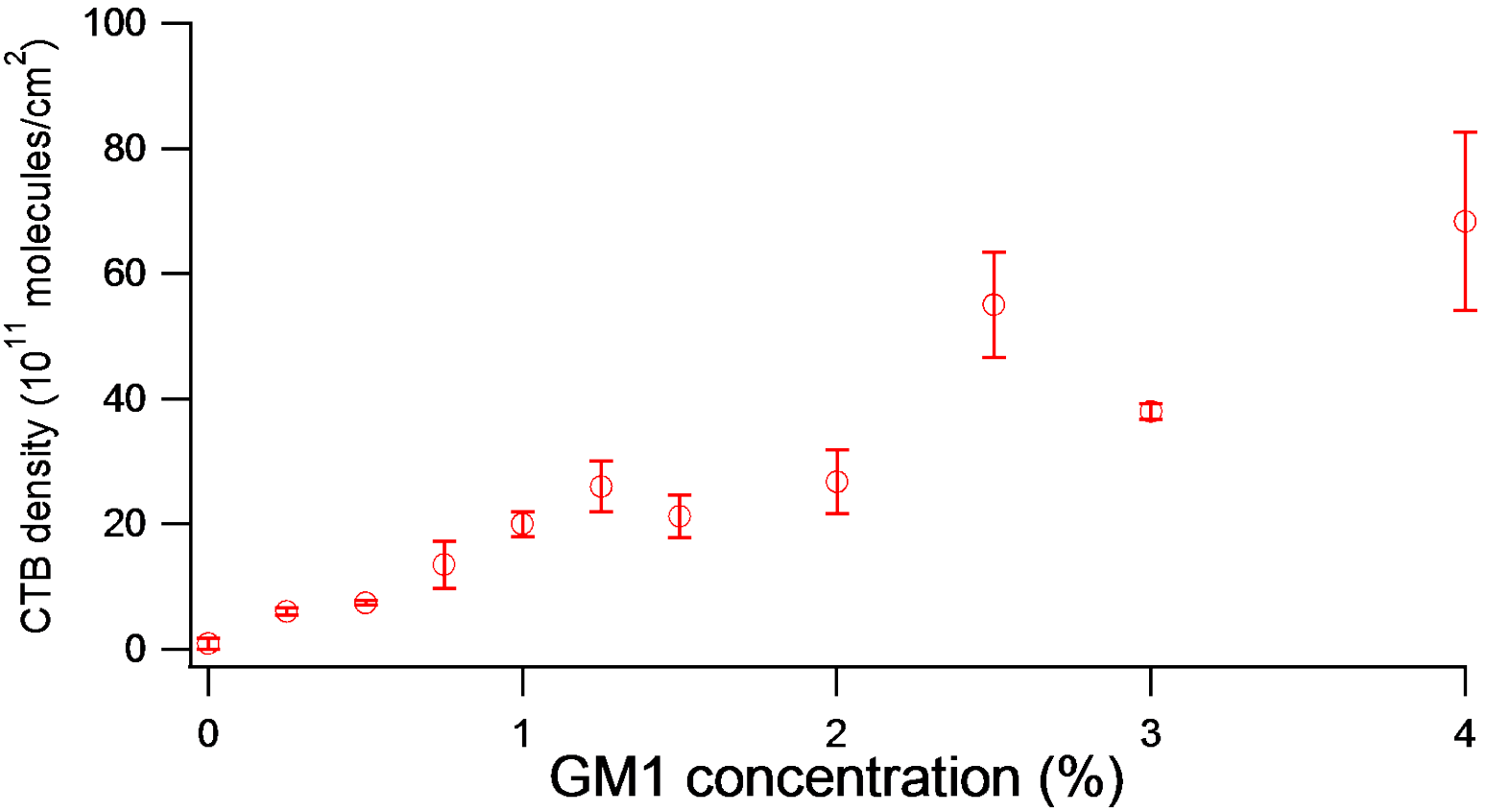


The dark area is silica-coated gold, the bright area is Cr

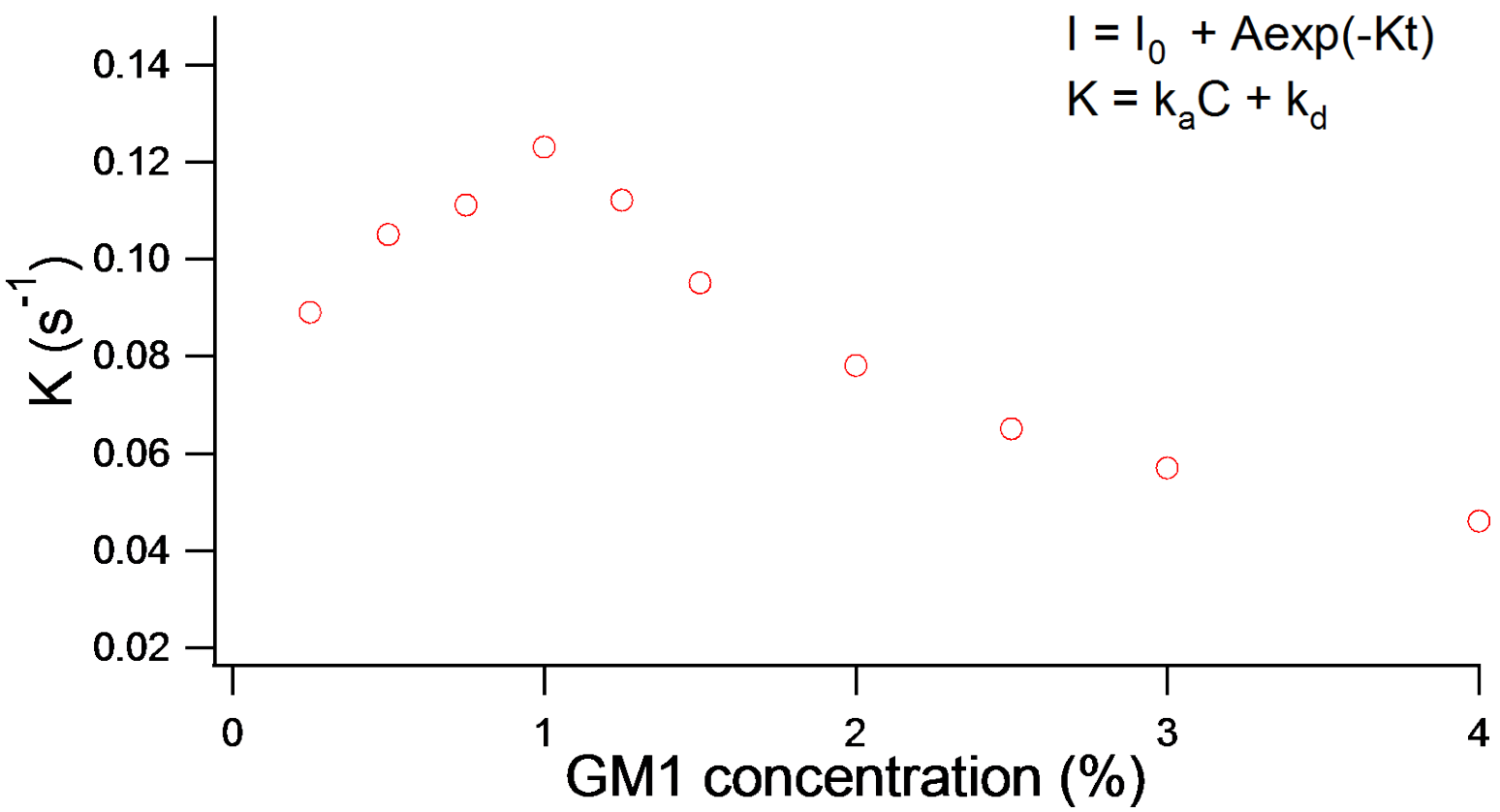
Example in glycomics: determining binding affinity of cholera toxin B-subunits (CTB) to ganglioside GM1



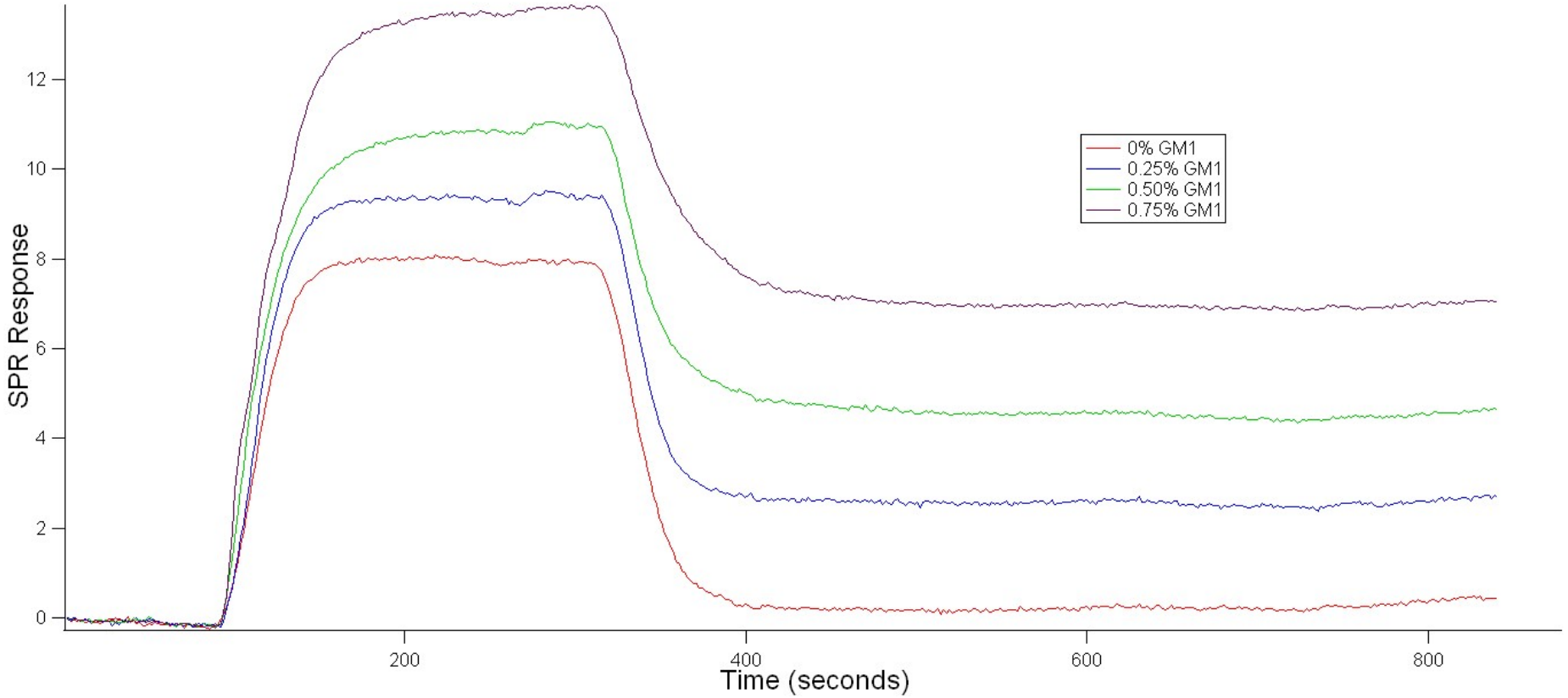
CTB binding with different concentrations of GM1

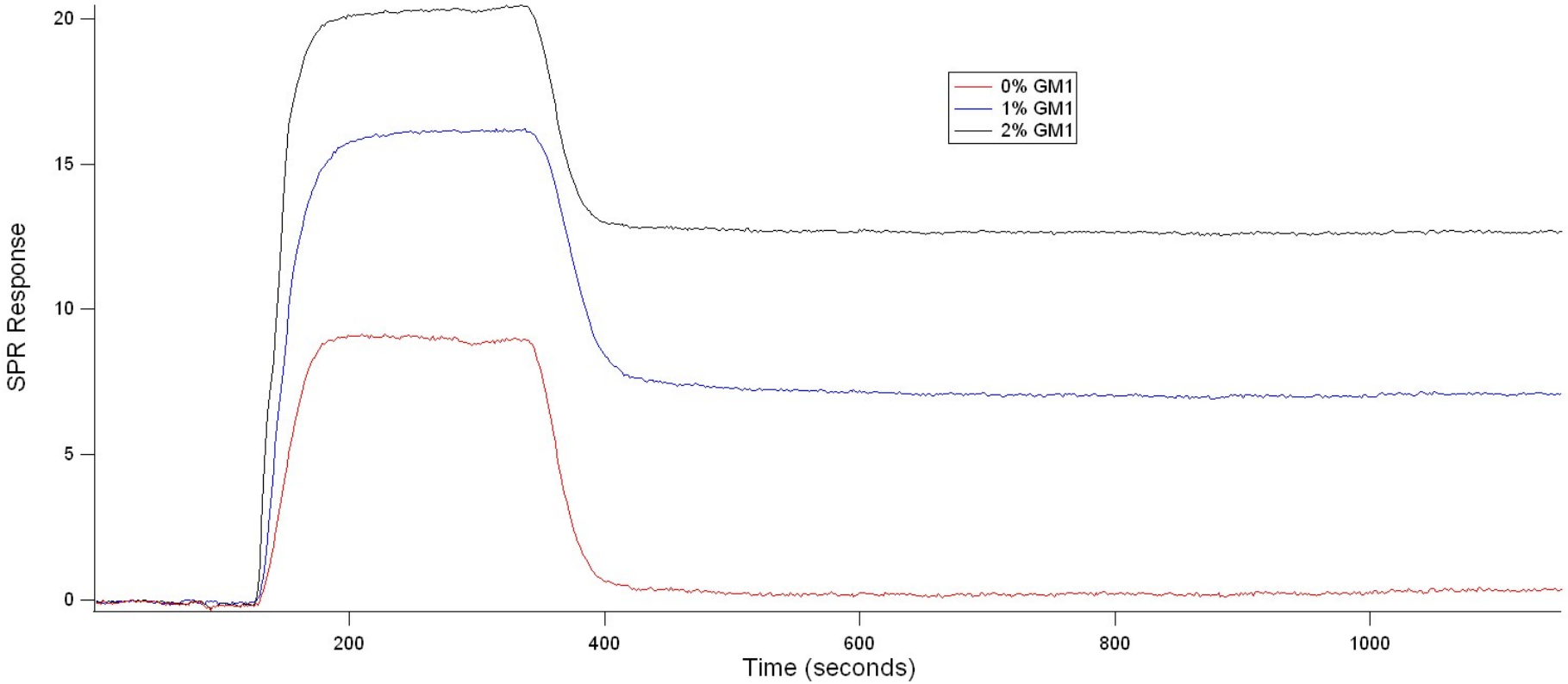


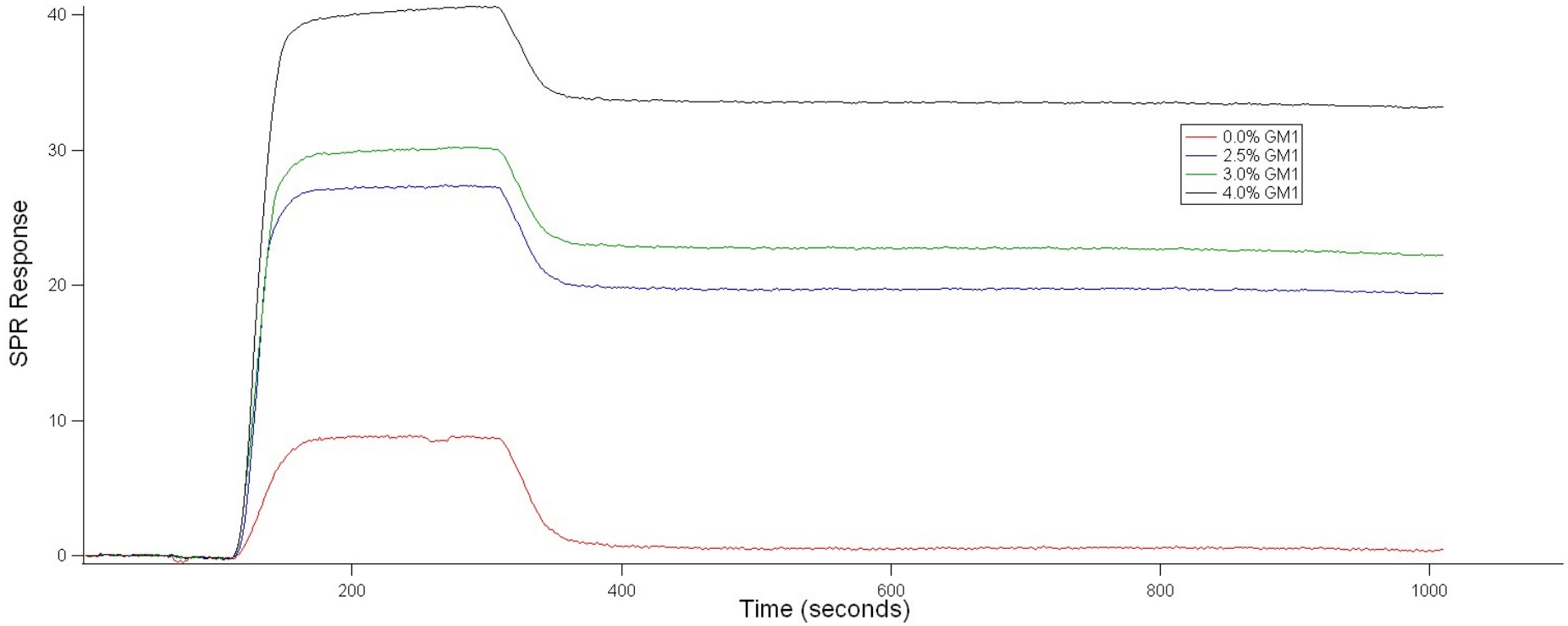
CTB binding with different concentration of GM1



Binding of CTB to GM1 Functionalized Lipid Membranes




0% GM1
1% GM1
2% GM1
SPR Response
Time (seconds)
0
5
10
15
20
200
400
600
800
1000


40
30
20
10
0
SPR Response
200
400
600
800
1000
Time (seconds)
0.0% GM1
2.5% GM1
3.0% GM1
4.0% GM1